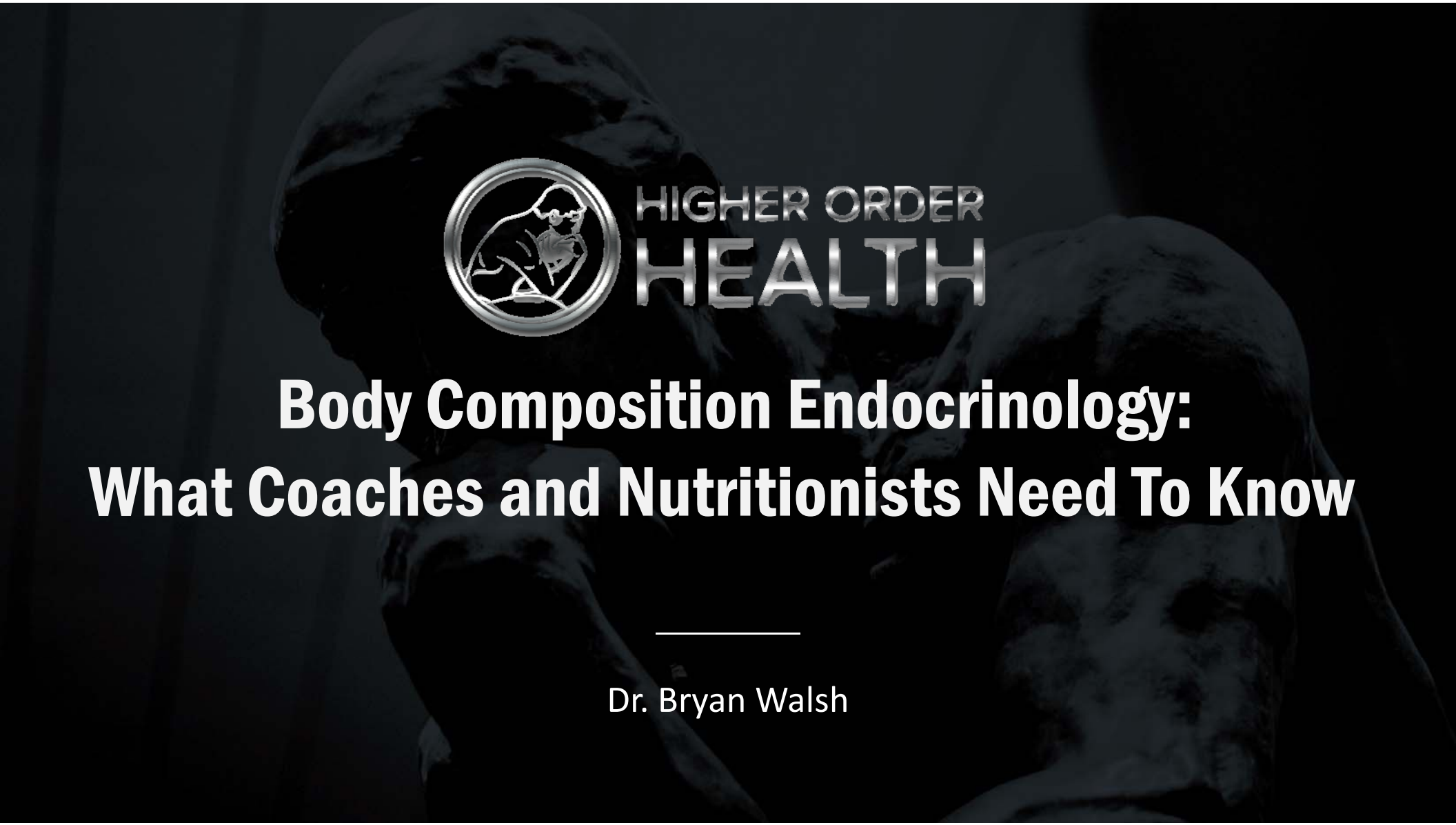
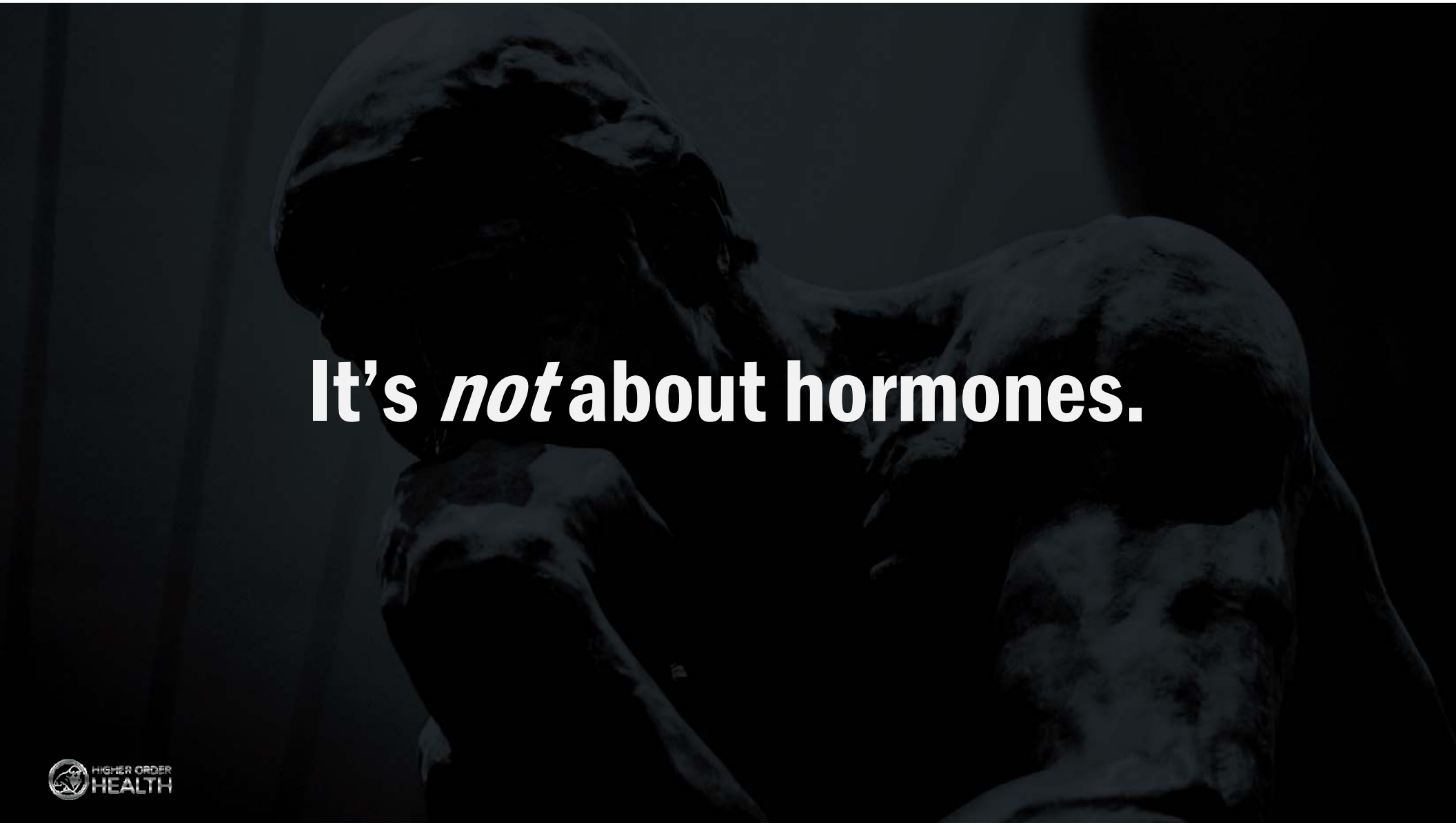
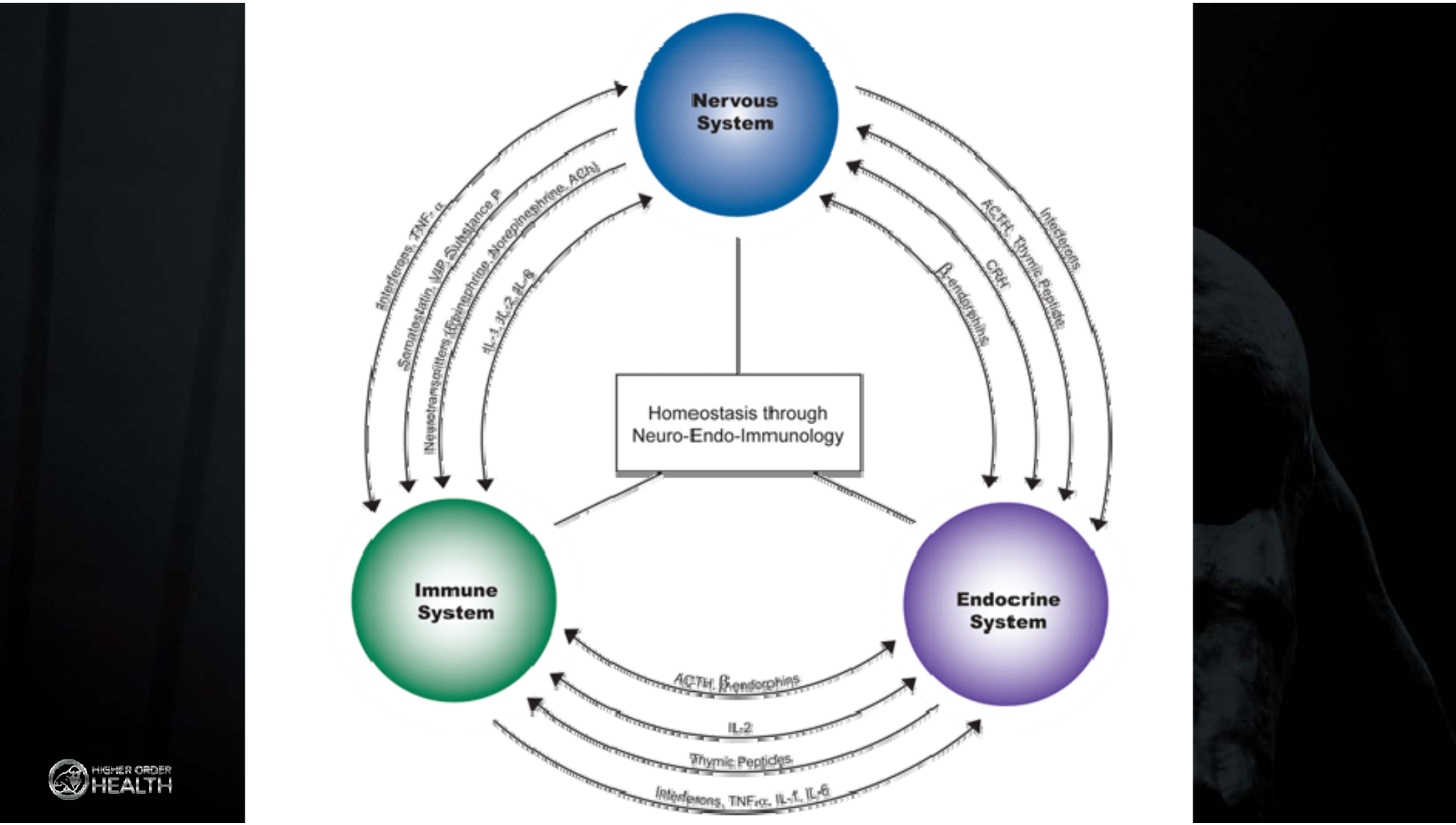


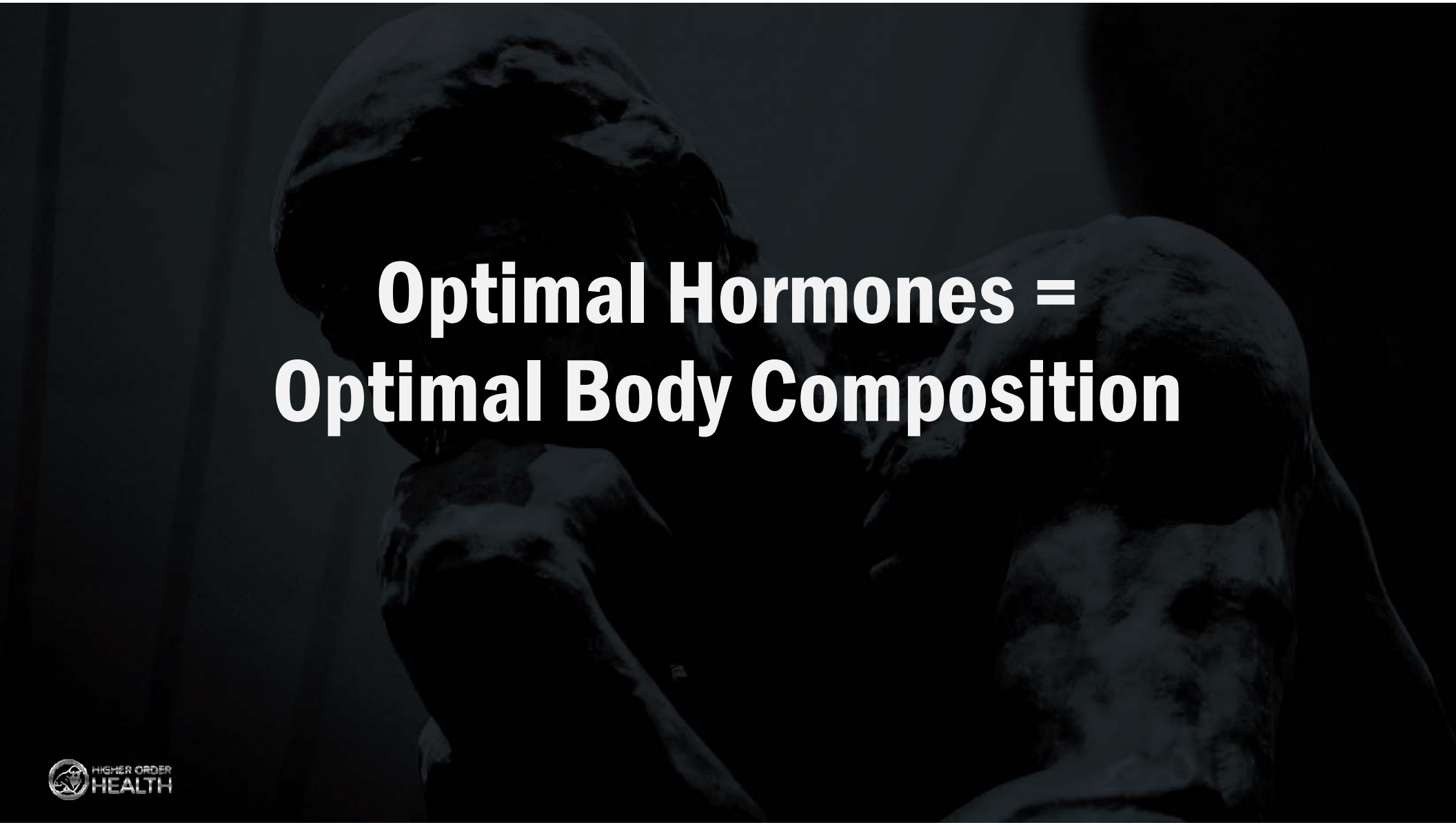
Body Composition Endocrinology: What Coaches and Nutritionists Need To Know

Dr. Bryan Walsh


It’s *not* about hormones.
HIGHER ORDER
HEALTH



HIGHER ORDER HEALTH


Optimal Hormones =
Optimal Body Composition
HIGHER ORDER
HEALTH

OVERVIEW

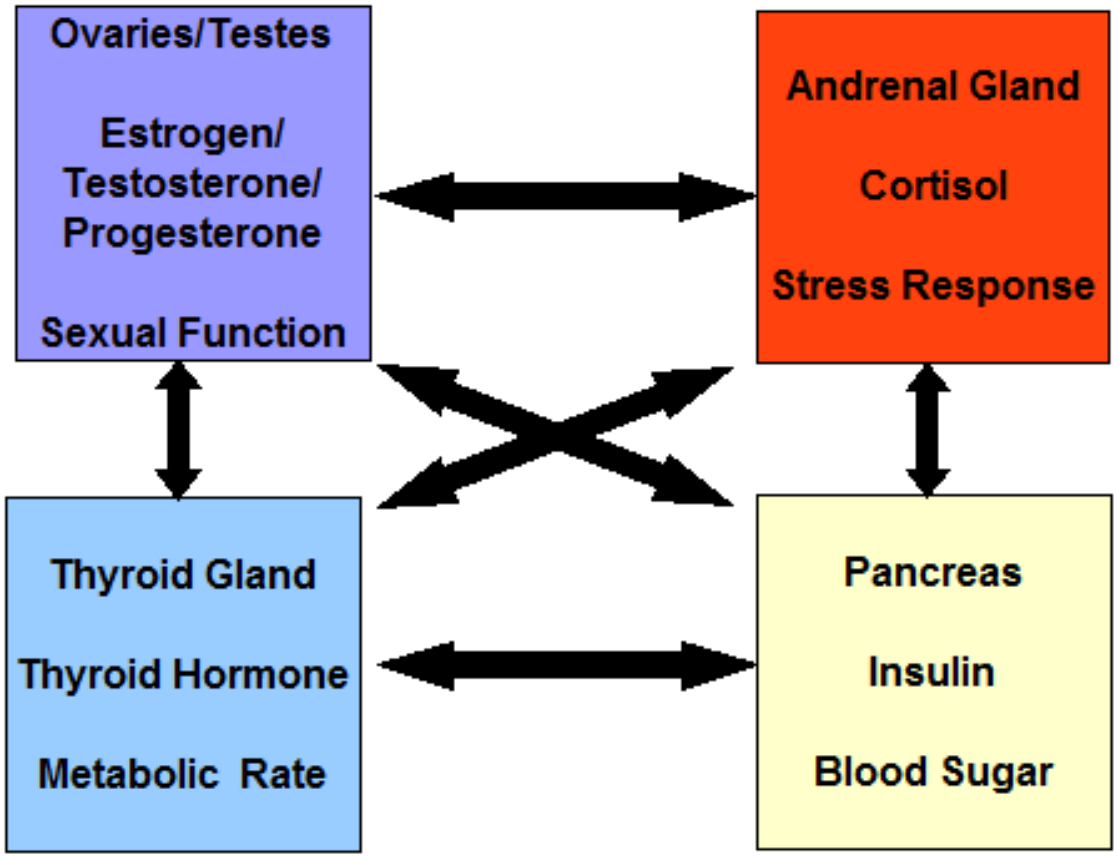
1. It’s about balance
2. Where’s the problem?
3. Gut health and hormones
4. Chemical toxins and hormones
5. Can we have sick fat cells?
6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

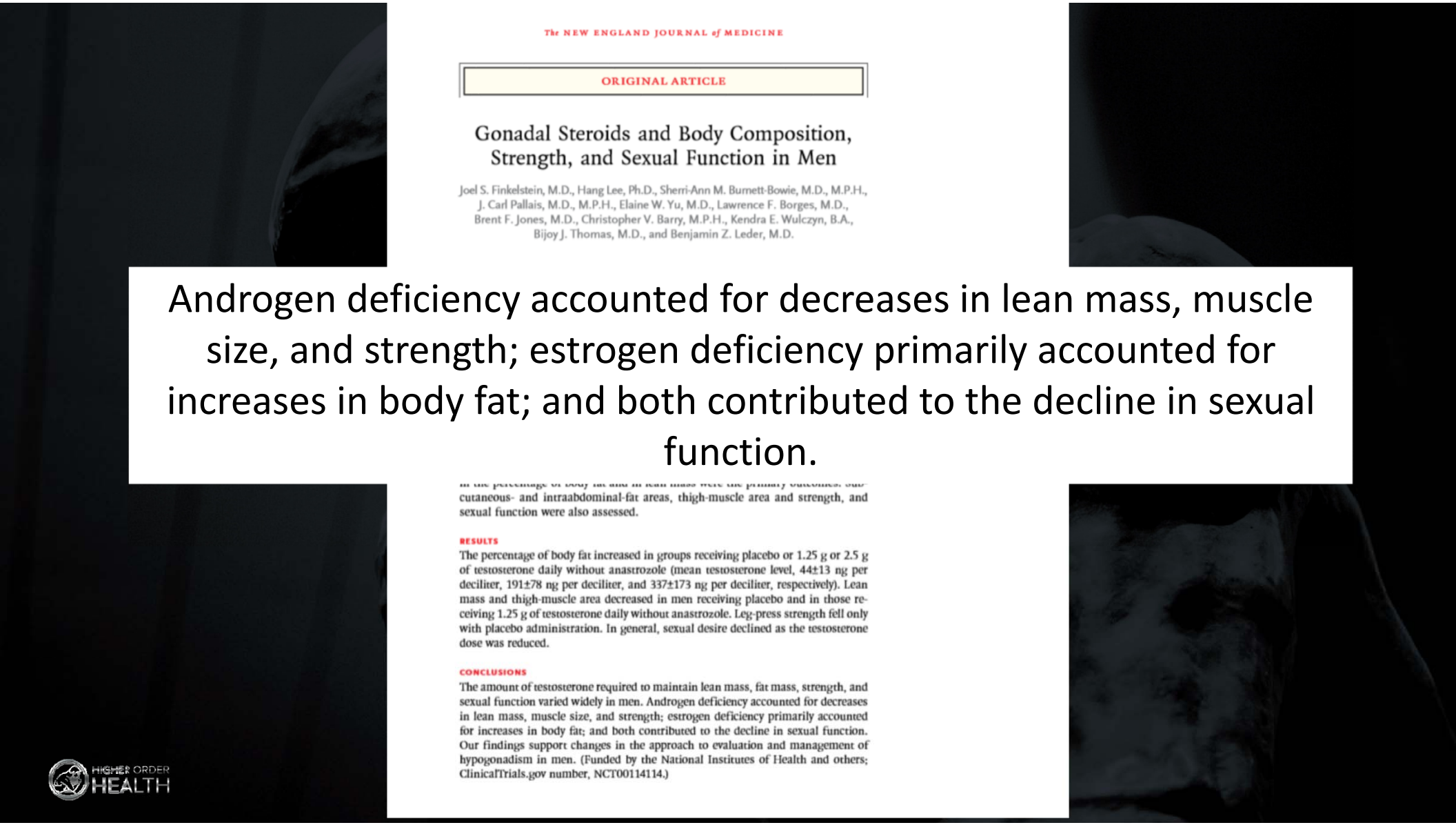
HIGHER ORDER HEALTH

It’s About Balance

HIGHER ORD
HEALTH

Hormonal Balance





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

Joel S. Finkelstein, M.D., Hang Lee, Ph.D., Sherri-Ann M. Burnett-Bowie, M.D., M.P.H., J. Carl Pallais, M.D., M.P.H., Elaine W. Yu, M.D., Lawrence F. Borges, M.D., Brent F. Jones, M.D., Christopher V. Barry, M.P.H., Kendra E. Wulczyn, B.A., Bijoy J. Thomas, M.D., and Benjamin Z. Leder, M.D.

Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function.

cutaneous- and intraabdominal-fat areas, thigh-muscle area and strength, and sexual function were also assessed.

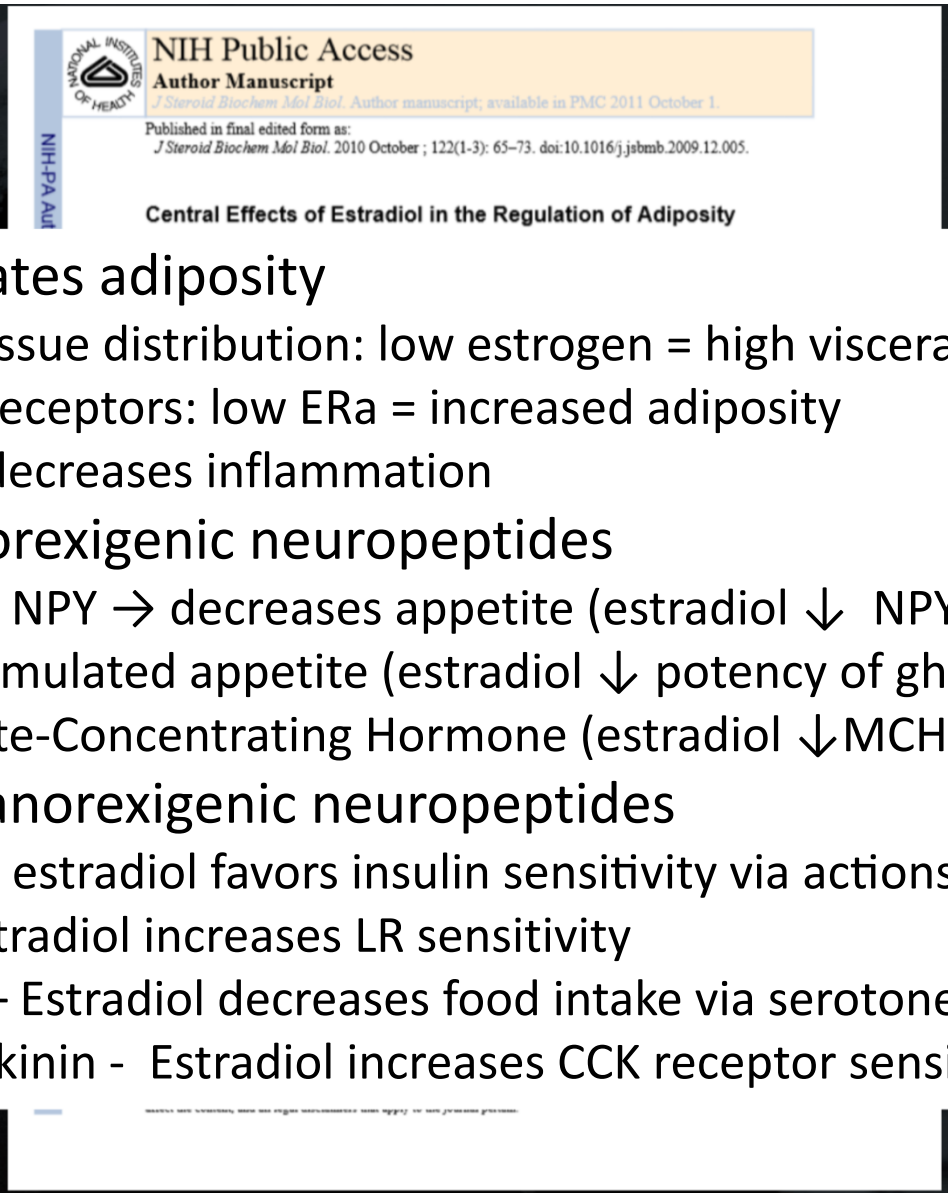
RESULTS

The percentage of body fat increased in groups receiving placebo or 1.25 g or 2.5 g of testosterone daily without anastrozole (mean testosterone level, 44±13 ng per deciliter, 191±78 ng per deciliter, and 337±173 ng per deciliter, respectively). Lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving 1.25 g of testosterone daily without anastrozole. Leg-press strength fell only with placebo administration. In general, sexual desire declined as the testosterone dose was reduced.

CONCLUSIONS

The amount of testosterone required to maintain lean mass, fat mass, strength, and sexual function varied widely in men. Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function. Our findings support changes in the approach to evaluation and management of hypogonadism in men. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00114114.)

HIGHER ORDER HEALTH



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Published in final edited form as:
J Steroid Biochem Mol Biol. 2010 October ; 122(1-3): 65–73. doi:10.1016/j.jsbmb.2009.12.005.

Central Effects of Estradiol in the Regulation of Adiposity

Estrogen regulates adiposity

- Adipose tissue distribution: low estrogen = high visceral fat
- Estrogen receptors: low ERa = increased adiposity
- Estrogen decreases inflammation

Interacts with orexigenic neuropeptides

- Decreases NPY → decreases appetite (estradiol ↓ NPY)
- Ghrelin stimulated appetite (estradiol ↓ potency of ghrelin)
- Melanocyte-Concentrating Hormone (estradiol ↓MCH)

Interacts with anorexigenic neuropeptides

- Insulin – ↓ estradiol favors insulin sensitivity via actions on brain
- Leptin – estradiol increases LR sensitivity
- Serotonin – Estradiol decreases food intake via serotonergic system
- Cholecystokinin - Estradiol increases CCK receptor sensitivity

ORIGINAL ARTICLE

Adipocyte Fatty Acid Storage Factors Enhance Subcutaneous Fat Storage in Postmenopausal Women

Sylvia Santosa[1,2] and Michael D. Jensen[1]

Postmenopausal women had lower postprandial FA oxidation, greater meal FA, and direct free FA (FFA) storage than premenopausal women, including two-fold greater meal FA storage in the femoral depot.

storage factors than from adipose tissue lipoprotein lipase activity. Our results suggest that female sex steroids, most likely estrogen, have important effects on adipose tissue FA storage and FA oxidation that could promote fat gain in postmenopausal women. *Diabetes* 62:775–782, 2013

Our results suggest that female sex steroids, most likely estrogen, have important effects on adipose tissue FA storage and FA oxidation that could promote fat gain in postmenopausal women.

These physiological measures were combined with measures of the adipose tissue content of a number of proteins/enzymes required for adipocyte FA storage.

From the [1]Endocrine Research Unit, Mayo Clinic, Rochester, Minnesota; and the [2]Department of Exercise Science, Concordia University, Montreal, Quebec, Canada.
Corresponding author: Michael D. Jensen, jensen@mayo.edu.
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DOI: 10.2337/db12-0912

needed for triglyceride synthesis.

We performed quantitative measures of meal-derived FA and direct FFA storage in adipose tissue and integrated these physiological assessments with information regarding

years from last menstrual period) or surgically (at least 2 years from salpingo-oophorectomy) participated in the research study. For the purposes of this report, we refer to this group as postmenopausal. To be included in the study, women could not have been using hormone replacement therapy for at least 2 years. Thirteen premenopausal women with normal serum estrogen concentrations (premenopausal) were recruited as age-matched and BMI-matched controls. All participants were healthy and weight was stable (±1.0 kg for >2 months before the study). Participants were excluded if they had diabetes, anemia, or were using antidepressants or other medications that could affect FA metabolism. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board of the Mayo Clinic.

Materials. [1-^{14}C]palmitate and [9,10-^{3}H]triolein were purchased from NEN Life Science Products (PerkinElmer, Boston, MA). $^{3}H_2O$ and [U-^{13}C]palmitate (both 99 atom percent pure) were purchased from Isotec (Miamisburg, OH).

Study design. All studies were conducted in the Mayo Clinical Research Unit. Before their inpatient study visit, total body water and body composition were

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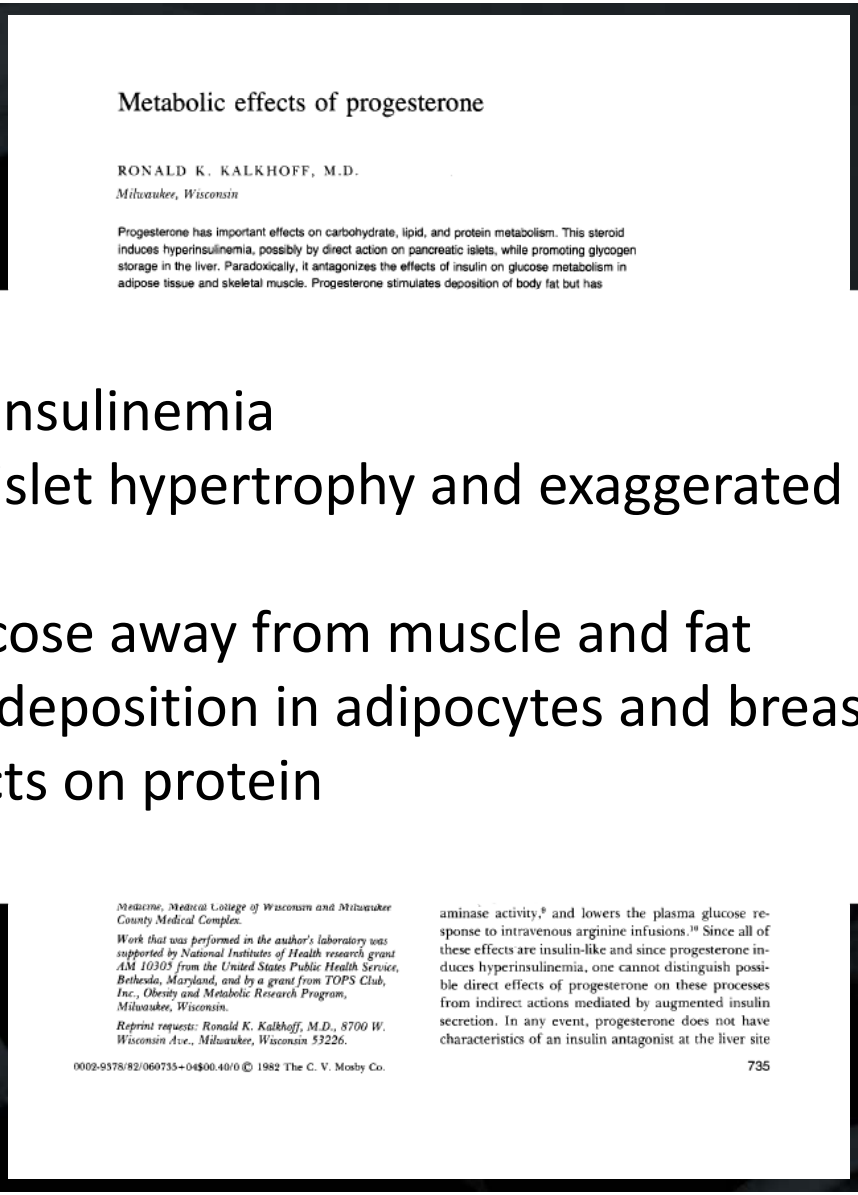


Metabolic effects of progesterone

RONALD K. KALKHOFF, M.D.

Milwaukee, Wisconsin

Progesterone has important effects on carbohydrate, lipid, and protein metabolism. This steroid induces hyperinsulinemia, possibly by direct action on pancreatic islets, while promoting glycogen storage in the liver. Paradoxically, it antagonizes the effects of insulin on glucose metabolism in adipose tissue and skeletal muscle. Progesterone stimulates deposition of body fat but has

Progesterone:

- Induces hyperinsulinemia
  - Pancreatic islet hypertrophy and exaggerated insulin response to glucose
  - Diverts glucose away from muscle and fat
- Stimulates fat deposition in adipocytes and breast tissue
- Catabolic effects on protein
- Hyperphagia

Medicine, Medical College of Wisconsin and Milwaukee County Medical Complex.

Work that was performed in the author's laboratory was supported by National Institutes of Health research grant AM 10305 from the United States Public Health Service, Bethesda, Maryland, and by a grant from TOPS Club, Inc., Obesity and Metabolic Research Program, Milwaukee, Wisconsin.

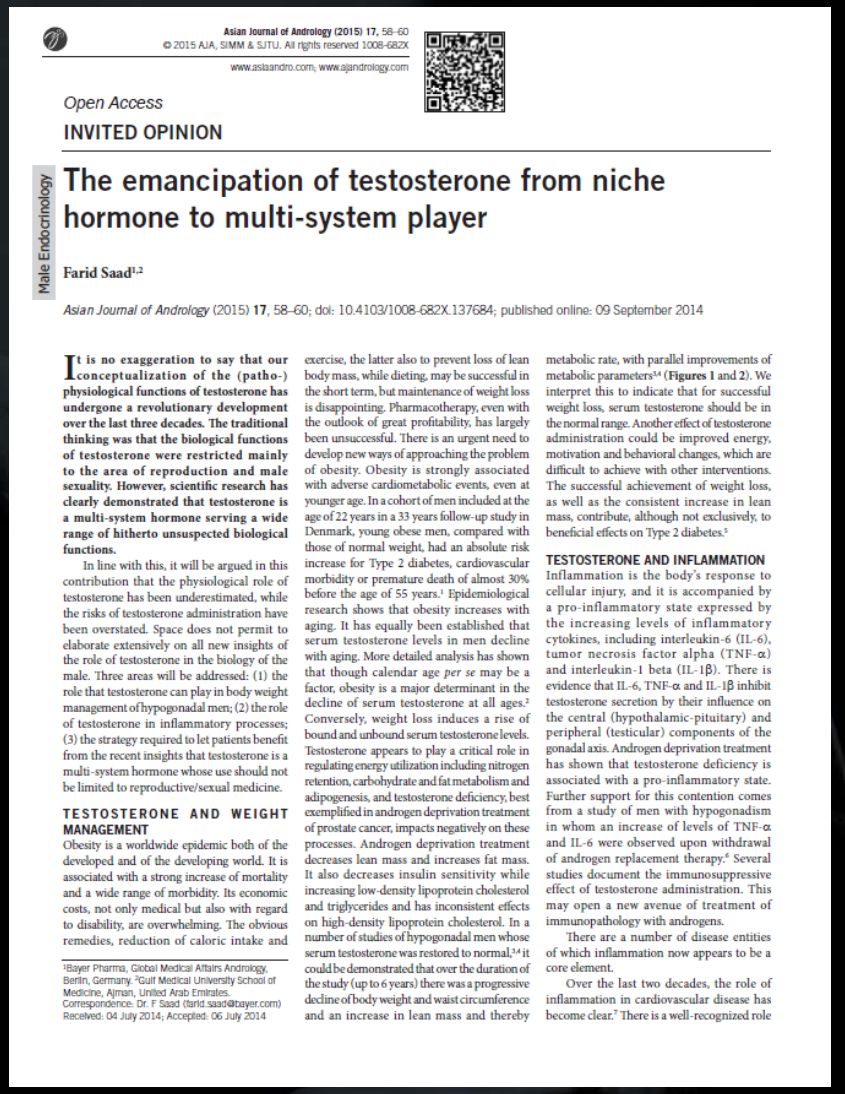
Reprint requests: Ronald K. Kalkhoff, M.D., 8700 W. Wisconsin Ave., Milwaukee, Wisconsin 53226.

0002-9378/82/060735+04$00.40/0

aminase activity,[8] and lowers the plasma glucose response to intravenous arginine infusions.[10] Since all of these effects are insulin-like and since progesterone induces hyperinsulinemia, one cannot distinguish possible direct effects of progesterone on these processes from indirect actions mediated by augmented insulin secretion. In any event, progesterone does not have characteristics of an insulin antagonist at the liver site

Hormone History

- The word “hormone” was first coined in 1905
- Insulin 1921
- Estrone 1929
- Progesterone 1934
- Testosterone 1935
- HPA Axis 1968



Asian Journal of Andrology (2015) 17, 58–60

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED OPINION

Male Endocrinology

The emancipation of testosterone from niche hormone to multi-system player

Farid Saad[1,2]

Asian Journal of Andrology (2015) **17**, 58–60; doi: 10.4103/1008-682X.137684; published online: 09 September 2014

It is no exaggeration to say that our conceptualization of the (patho-) physiological functions of testosterone has undergone a revolutionary development over the last three decades. The traditional thinking was that the biological functions of testosterone were restricted mainly to the area of reproduction and male sexuality. However, scientific research has clearly demonstrated that testosterone is a multi-system hormone serving a wide range of hitherto unsuspected biological functions.

In line with this, it will be argued in this contribution that the physiological role of testosterone has been underestimated, while the risks of testosterone administration have been overstated. Space does not permit to elaborate extensively on all new insights of the role of testosterone in the biology of the male. Three areas will be addressed: (1) the role that testosterone can play in body weight management of hypogonadal men; (2) the role of testosterone in inflammatory processes; (3) the strategy required to let patients benefit from the recent insights that testosterone is a multi-system hormone whose use should not be limited to reproductive/sexual medicine.

TESTOSTERONE AND WEIGHT MANAGEMENT

Obesity is a worldwide epidemic both of the developed and of the developing world. It is associated with a strong increase of mortality and a wide range of morbidity. Its economic costs, not only medical but also with regard to disability, are overwhelming. The obvious remedies, reduction of caloric intake and exercise, the latter also to prevent loss of lean body mass, while dieting, may be successful in the short term, but maintenance of weight loss is disappointing. Pharmacotherapy, even with the outlook of great profitability, has largely been unsuccessful. There is an urgent need to develop new ways of approaching the problem of obesity. Obesity is strongly associated with adverse cardiometabolic events, even at younger age. In a cohort of men included at the age of 22 years in a 33 years follow-up study in Denmark, young obese men, compared with those of normal weight, had an absolute risk increase for Type 2 diabetes, cardiovascular morbidity or premature death of almost 30% before the age of 55 years.[1] Epidemiological research shows that obesity increases with aging. It has equally been established that serum testosterone levels in men decline with aging. More detailed analysis has shown that though calendar age *per se* may be a factor, obesity is a major determinant in the decline of serum testosterone at all ages.[2] Conversely, weight loss induces a rise of bound and unbound serum testosterone levels. Testosterone appears to play a critical role in regulating energy utilization including nitrogen retention, carbohydrate and fat metabolism and adipogenesis, and testosterone deficiency, best exemplified in androgen deprivation treatment of prostate cancer, impacts negatively on these processes. Androgen deprivation treatment decreases lean mass and increases fat mass. It also decreases insulin sensitivity while increasing low-density lipoprotein cholesterol and triglycerides and has inconsistent effects on high-density lipoprotein cholesterol. In a number of studies of hypogonadal men whose serum testosterone was restored to normal,[3,4] it could be demonstrated that over the duration of the study (up to 6 years) there was a progressive decline of body weight and waist circumference and an increase in lean mass and thereby metabolic rate, with parallel improvements of metabolic parameters[3,4] (**Figures 1** and **2**). We interpret this to indicate that for successful weight loss, serum testosterone should be in the normal range. Another effect of testosterone administration could be improved energy, motivation and behavioral changes, which are difficult to achieve with other interventions. The successful achievement of weight loss, as well as the consistent increase in lean mass, contribute, although not exclusively, to beneficial effects on Type 2 diabetes.[5]

TESTOSTERONE AND INFLAMMATION

Inflammation is the body's response to cellular injury, and it is accompanied by a pro-inflammatory state expressed by the increasing levels of inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β). There is evidence that IL-6, TNF-α and IL-1β inhibit testosterone secretion by their influence on the central (hypothalamic-pituitary) and peripheral (testicular) components of the gonadal axis. Androgen deprivation treatment has shown that testosterone deficiency is associated with a pro-inflammatory state. Further support for this contention comes from a study of men with hypogonadism in whom an increase of levels of TNF-α and IL-6 were observed upon withdrawal of androgen replacement therapy.[6] Several studies document the immunosuppressive effect of testosterone administration. This may open a new avenue of treatment of immunopathology with androgens.

There are a number of disease entities of which inflammation now appears to be a core element.

Over the last two decades, the role of inflammation in cardiovascular disease has become clear.[7] There is a well-recognized role

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HIGHER ORDER HEALTH

Journal of Anatomy

J. Anat. (2013) 223, pp321–328 doi: 10.1111/joa.12087

Anatomy of the anterolateral ligament of the knee

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[2]Department of Development and Regeneration, Faculty of Medicine@Kulak, Catholic University Leuven, Kortrijk, Belgium
[3]Department of Orthopedic Surgery & Traumatology, University Hospital Gent, Ghent, Belgium
[4]Antwerp Orthopedic Center, Monica Hospitals, Antwerp, Belgium

Abstract

In 1879, the French surgeon Segond described the existence of a 'pearly, resistant, fibrous band' at the anterolateral aspect of the human knee, attached to the eponymous Segond fracture. To date, the enigma surrounding this anatomical structure is reflected in confusing names such as '(mid-third) lateral capsular ligament', 'capsulo-osseous layer of the iliotibial band' or 'anterolateral ligament', and no clear anatomical description has yet been provided. In this study, the presence and characteristics of Segond's 'pearly band', hereafter termed anterolateral ligament (ALL), was investigated in 41 unpaired, human cadaveric knees. The femoral and tibial attachment of the ALL, its course and its relationship with nearby anatomical structures were studied both qualitatively and quantitatively. In all but one of 41 cadaveric knees (97%), the ALL was found as a well-defined ligamentous structure, clearly distinguishable from the anterolateral joint capsule. The origin of the ALL was situated at the prominence of the lateral femoral epicondyle, slightly anterior to the origin of the lateral collateral ligament, although connecting fibers between the two structures were observed. The ALL showed an oblique course to the anterolateral aspect of the proximal tibia, with firm attachments to the lateral meniscus, thus enveloping the inferior lateral geniculate artery and vein. Its insertion on the anterolateral tibia was grossly located midway between Gerdy's tubercle and the tip of the fibular head, definitely separate from the iliotibial band (ITB). The ALL was found to be a distinct ligamentous structure at the anterolateral aspect of the human knee with consistent origin and insertion site features. By providing a detailed anatomical characterization of the ALL, this study clarifies the long-standing enigma surrounding the existence of a ligamentous structure connecting the femur with the anterolateral tibia. Given its structure and anatomic location, the ALL is hypothesized to control internal tibial rotation and thus to affect the pivot shift phenomenon, although further studies are needed to investigate its biomechanical function.

Key words: anatomy; anterior cruciate ligament; anterolateral ligament; pivot-shift; Segond fracture.

Introduction

In 1879, years before the discovery of X-rays, Dr. Paul Segond described a remarkably constant avulsion fracture pattern at the anterolateral proximal tibia as a result of forced internal rotation at the knee (Segond, 1879). This eponymous Segond fracture was reported to occur in the tibial region 'above and behind the tubercle of Gerdy'. At this anatomical location, he furthermore designated the existence of 'a pearly, resistant, fibrous band which invariably showed extreme amounts of tension during forced internal rotation (of the knee)'.

Inspired by the work of Dr. Jack Hughston, the first correlation of the Segond fracture with the presence of significant knee instability was demonstrated by Woods et al. (1979). In all of the four acute cases with a positive 'lateral capsular sign' on X-ray, a concomitant rupture of the anterior cruciate ligament (ACL) was demonstrated. This study, together with the work of Goldman et al. (1988) and Hess et al. (1994) has founded the current belief that Segond fractures are pathognomonic for ACL tears.

Whereas Segond described a 'pearly, fibrous band' attached to his flake fracture, later literature has only rarely mentioned the presence of a ligamentous structure connecting the femur with the anterolateral tibia. These sporadic reports mention the 'anterior band of the lateral collateral ligament' (Irvine et al. 1987), the '(mid-third) lateral capsular ligament' (Hughston et al. 1976b; Johnson, 1979; Haims

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Clinical Anatomy 29:256–263 (2016)

ORIGINAL COMMUNICATION

A Newly Discovered Muscle:
The Tensor of the Vastus Intermedius

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[2]The University of Western Australia, Perth, Australia
[3]Department of Anatomy, University of Zürich-Irchel, Zürich, Switzerland
[4]Department of Anatomy, University of Fribourg, Fribourg, Switzerland

The quadriceps femoris is traditionally described as a muscle group composed of the rectus femoris and the three vasti. However, clinical experience and investigations of anatomical specimens are not consistent with the textbook description. We have found a second tensor-like muscle between the vastus lateralis (VL) and the vastus intermedius (VI), hereafter named the tensor VI (TVI). The aim of this study was to clarify whether this intervening muscle was a variation of the VL or the VI, or a separate head of the extensor apparatus. Twenty-six cadaveric lower limbs were investigated. The architecture of the quadriceps femoris was examined with special attention to innervation and vascularization patterns. All muscle components were traced from origin to insertion and their affiliations were determined. A TVI was found in all dissections. It was supplied by independent muscular and vascular branches of the femoral nerve and lateral circumflex femoral artery. Further distally, the TVI combined with an aponeurosis merging separately into the quadriceps tendon and inserting on the medial aspect of the patella. Four morphological types of TVI were distinguished: Independent-type (11/26), VI-type (6/26), VL-type (5/26), and Common-type (4/26). This study demonstrated that the quadriceps femoris is architecturally different from previous descriptions: there is an additional muscle belly between the VI and VL, which cannot be clearly assigned to the former or the latter. Distal exposure shows that this muscle belly becomes its own aponeurosis, which continues distally as part of the quadriceps tendon. Clin. Anat. 29:256–263, 2016. © 2016 Wiley Periodicals, Inc.

Key words: quadriceps femorismuscle group; quadriceps tendon; tensor vastus intermedius TVI; quinticeps; extensor apparatus of the knee joint

INTRODUCTION

The quadriceps femoris is traditionally described as a muscle composed of the rectus femoris and the three vasti, the lateralis, intermedius and medialis, which arise independently and blend into the common quadriceps tendon (Putz and Papst, 2008; Platzer et al., 2010; Schünke et al. 2014; Paternoster, 2012). However, clinical experience and anatomical studies do not confirm textbook descriptions of the vastus lateralis (VL) and intermedius (VI) muscles. After careful

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PEOPLE DON´T WANT TO HEAR THE TRUTH BECAUSE THEY DON´T WANT THEIR ILLUSIONS DESTROYED.

— FRIEDRICH NIETZSCHE

Stupidity is not the lack of knowledge, but the illusion of having it.

Grigore Iulian

meetville.com

HIGHER ORDER HEALTH


HIGHER ORDER
HEALTH

OVERVIEW

1. It’s about balance
2. Where’s the problem?
3. Gut health and hormones
4. Chemical toxins and hormones
5. Can we have sick fat cells?
6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

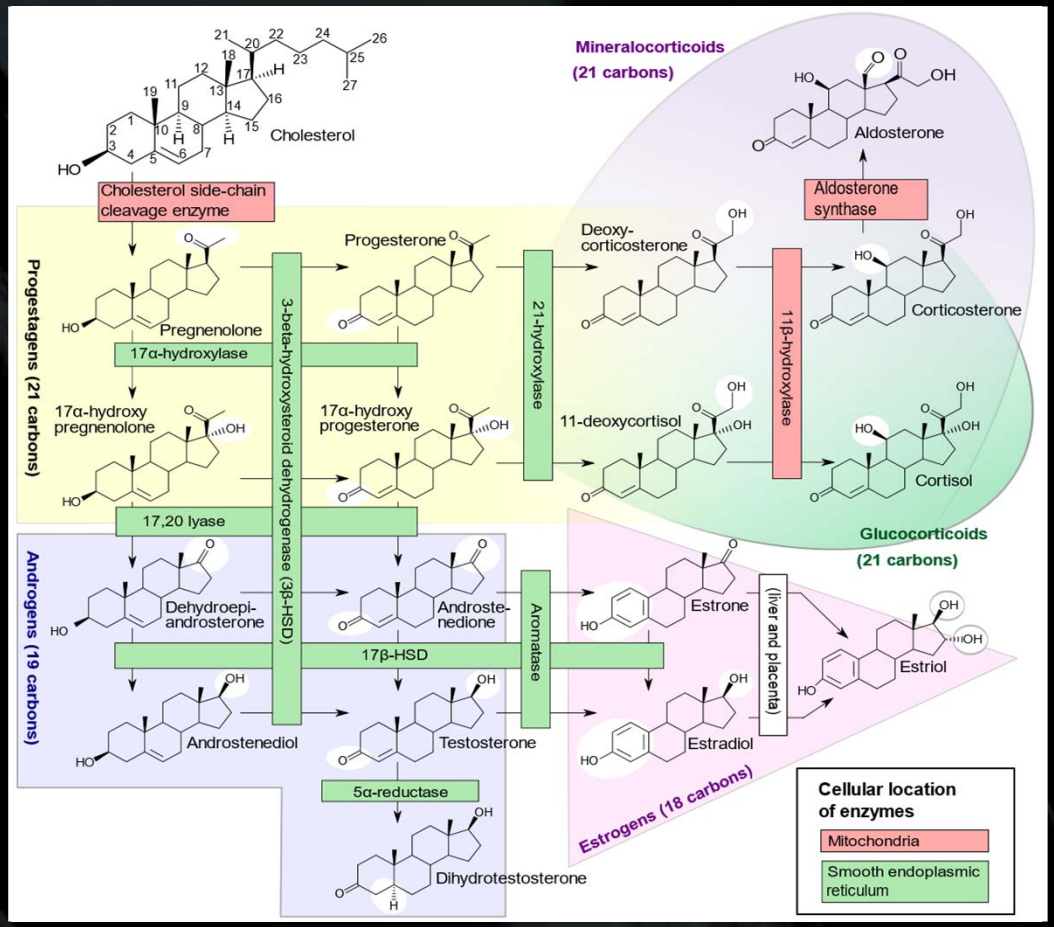
HIGHER ORDER HEALTH

Where's the Problem?

HIGHER ORDER HEALTH

Basic Endocrinology Principles

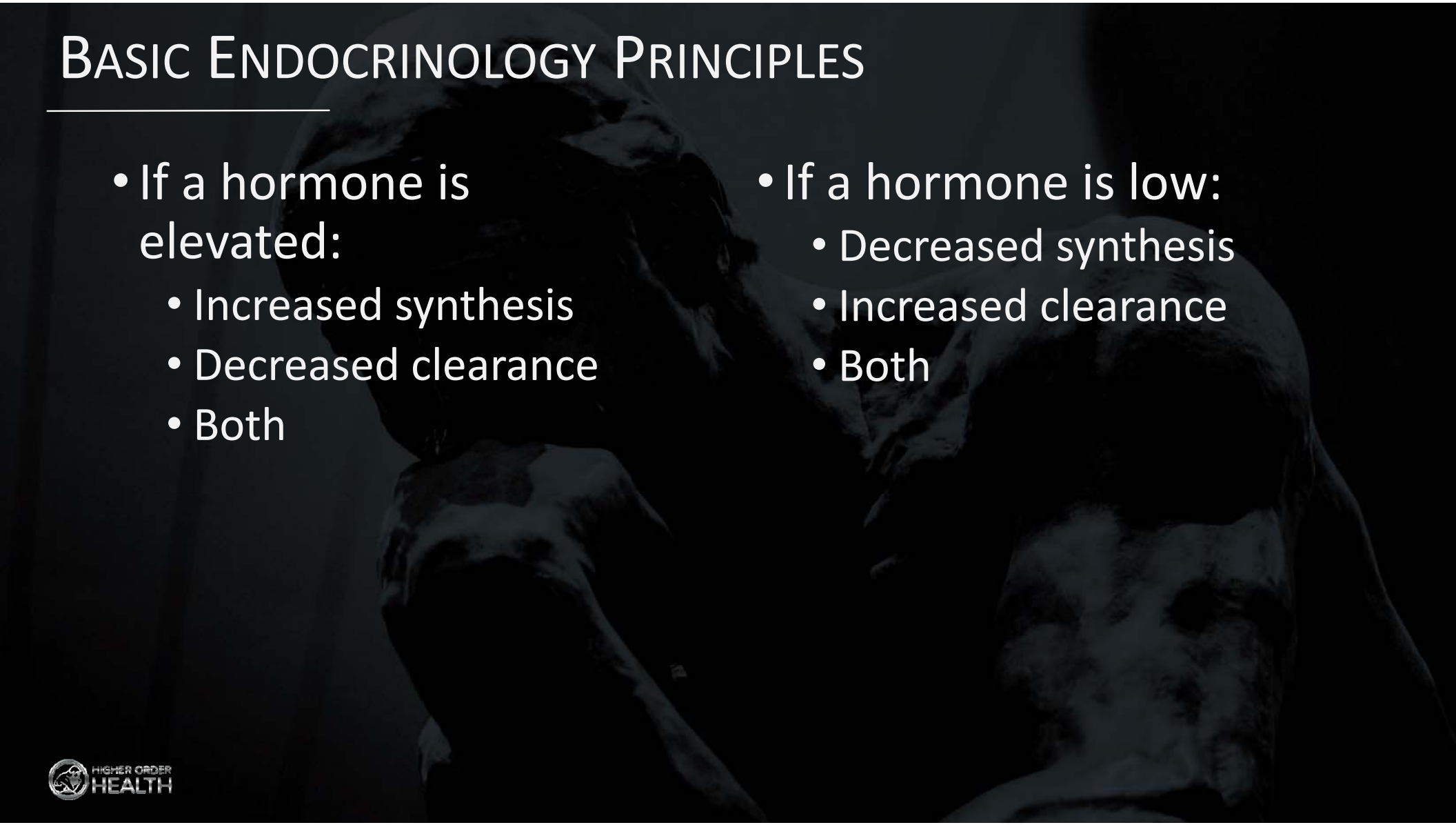
1. Measuring hormones, but *evaluating* enzymes
   - Synthesis
   - Conversion
   - Clearance



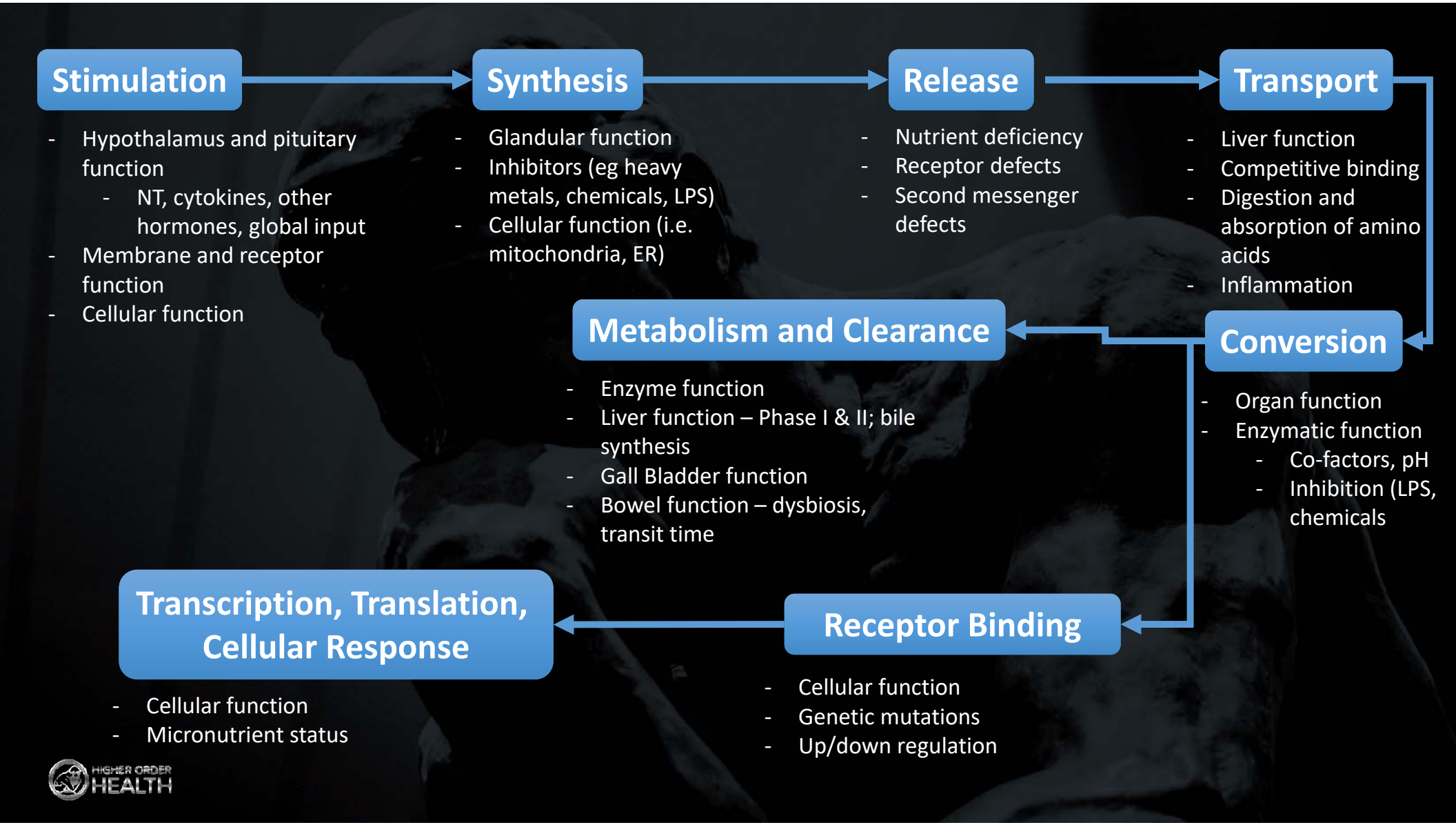
HIGHER ORDER HEALTH

Basic Endocrinology Principles

- If a hormone is elevated:
  - Increased synthesis
  - Decreased clearance
  - Both
- If a hormone is low:
  - Decreased synthesis
  - Increased clearance
  - Both



HIGHER ORDER HEALTH


Stimulation
- Hypothalamus and pituitary function
  - NT, cytokines, other hormones, global input
- Membrane and receptor function
- Cellular function
Synthesis
- Glandular function
- Inhibitors (eg heavy metals, chemicals, LPS)
- Cellular function (i.e. mitochondria, ER)
Release
- Nutrient deficiency
- Receptor defects
- Second messenger defects
Transport
- Liver function
- Competitive binding
- Digestion and absorption of amino acids
- Inflammation
Conversion
- Organ function
- Enzymatic function
  - Co-factors, pH
  - Inhibition (LPS, chemicals
Metabolism and Clearance
- Enzyme function
- Liver function – Phase I & II; bile synthesis
- Gall Bladder function
- Bowel function – dysbiosis, transit time
Receptor Binding
- Cellular function
- Genetic mutations
- Up/down regulation
Transcription, Translation, Cellular Response
- Cellular function
- Micronutrient status
HIGHER ORDER HEALTH

Basic Endocrinology Principles

- Antagonism – opposite effects
  - Calcitonin, parathyroid hormone
  - Glucagon, insulin
- Synergistic
  - Testosterone and FSH on spermatogenesis
- Permissive – presence of one hormone increases action of another
  - Thyroid and epinephrine
  - Cortisol and GH

Basic Endocrinology Principles

- Secretion
  - Hypo
    - Glandular dysfunction
    - Enzyme deficiency
  - Hyper
    - Primary – by itself (tumor, autoimmune, i.e. graves)
    - Secondary – excessive stimulation by other trophic hormone
- Responsiveness
  - Hypo
    - down-regulation or deficiency of receptors (or abnormal)
    - Intracellular issues (eg insulin resistance)
    - Poor conversion – PCOS – testosterone doesn't convert to E2
  - Hyper
    - Too much thyroid hormone, makes epi more sensitive
    - Increased insulin sensitivity

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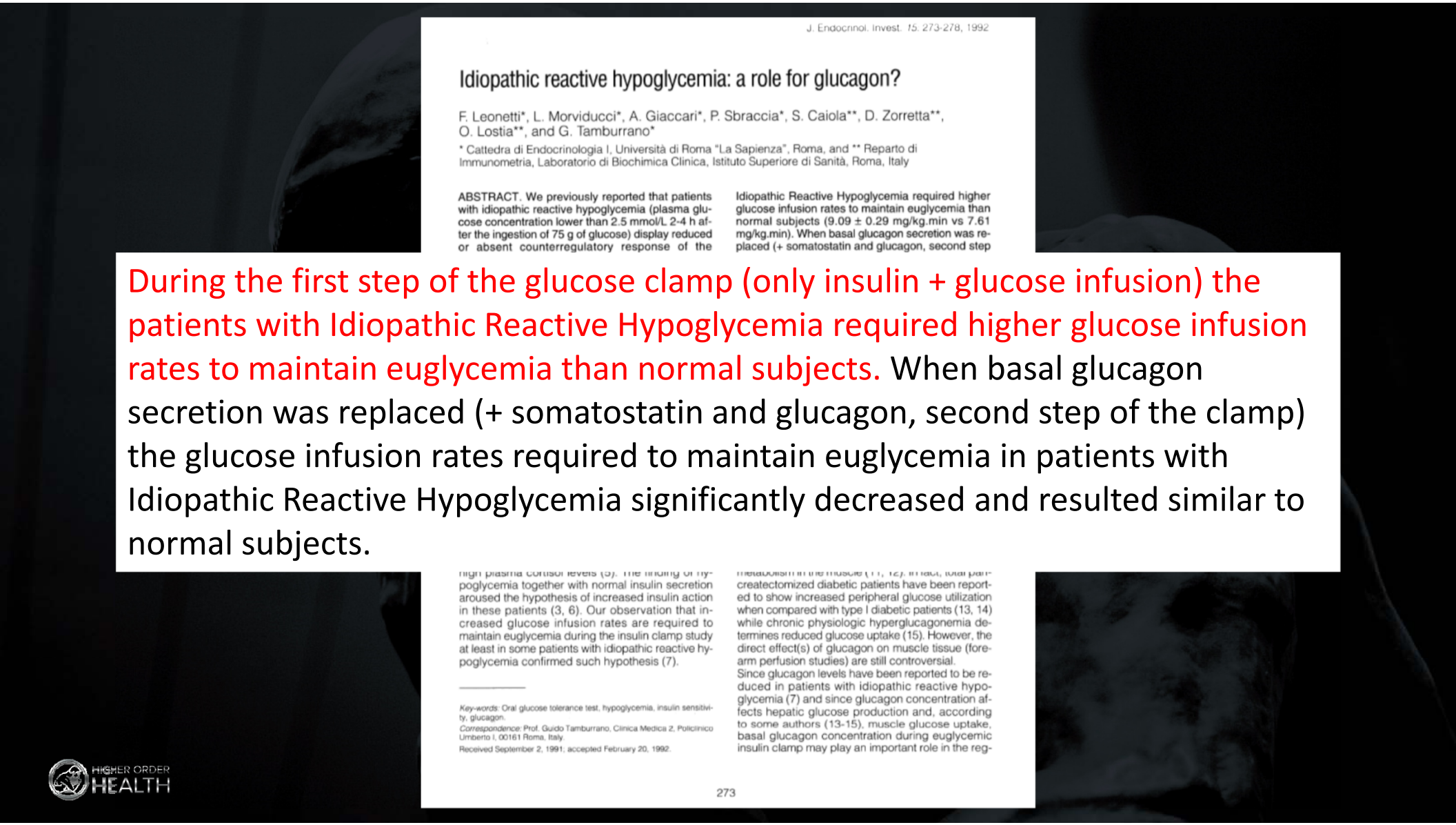

J. Endocrinol. Invest. 15: 273-278, 1992

Idiopathic reactive hypoglycemia: a role for glucagon?

F. Leonetti*, L. Morviducci*, A. Giaccari*, P. Sbraccia*, S. Caiola**, D. Zorretta**, O. Lostia**, and G. Tamburrano*

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ABSTRACT. We previously reported that patients with idiopathic reactive hypoglycemia (plasma glucose concentration lower than 2.5 mmol/L 2-4 h after the ingestion of 75 g of glucose) display reduced or absent counterregulatory response of the

Idiopathic Reactive Hypoglycemia required higher glucose infusion rates to maintain euglycemia than normal subjects (9.09 ± 0.29 mg/kg.min vs 7.61 mg/kg.min). When basal glucagon secretion was replaced (+ somatostatin and glucagon, second step

During the first step of the glucose clamp (only insulin + glucose infusion) the patients with Idiopathic Reactive Hypoglycemia required higher glucose infusion rates to maintain euglycemia than normal subjects. When basal glucagon secretion was replaced (+ somatostatin and glucagon, second step of the clamp) the glucose infusion rates required to maintain euglycemia in patients with Idiopathic Reactive Hypoglycemia significantly decreased and resulted similar to normal subjects.

high plasma cortisol levels (5). The finding of hypoglycemia together with normal insulin secretion aroused the hypothesis of increased insulin action in these patients (3, 6). Our observation that increased glucose infusion rates are required to maintain euglycemia during the insulin clamp study at least in some patients with idiopathic reactive hypoglycemia confirmed such hypothesis (7).

Key-words: Oral glucose tolerance test, hypoglycemia, insulin sensitivity, glucagon.

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metabolism in the muscle (11, 12). In fact, total pancreatectomized diabetic patients have been reported to show increased peripheral glucose utilization when compared with type I diabetic patients (13, 14) while chronic physiologic hyperglucagonemia determines reduced glucose uptake (15). However, the direct effect(s) of glucagon on muscle tissue (forearm perfusion studies) are still controversial.

Since glucagon levels have been reported to be reduced in patients with idiopathic reactive hypoglycemia (7) and since glucagon concentration affects hepatic glucose production and, according to some authors (13-15), muscle glucose uptake, basal glucagon concentration during euglycemic insulin clamp may play an important role in the reg-

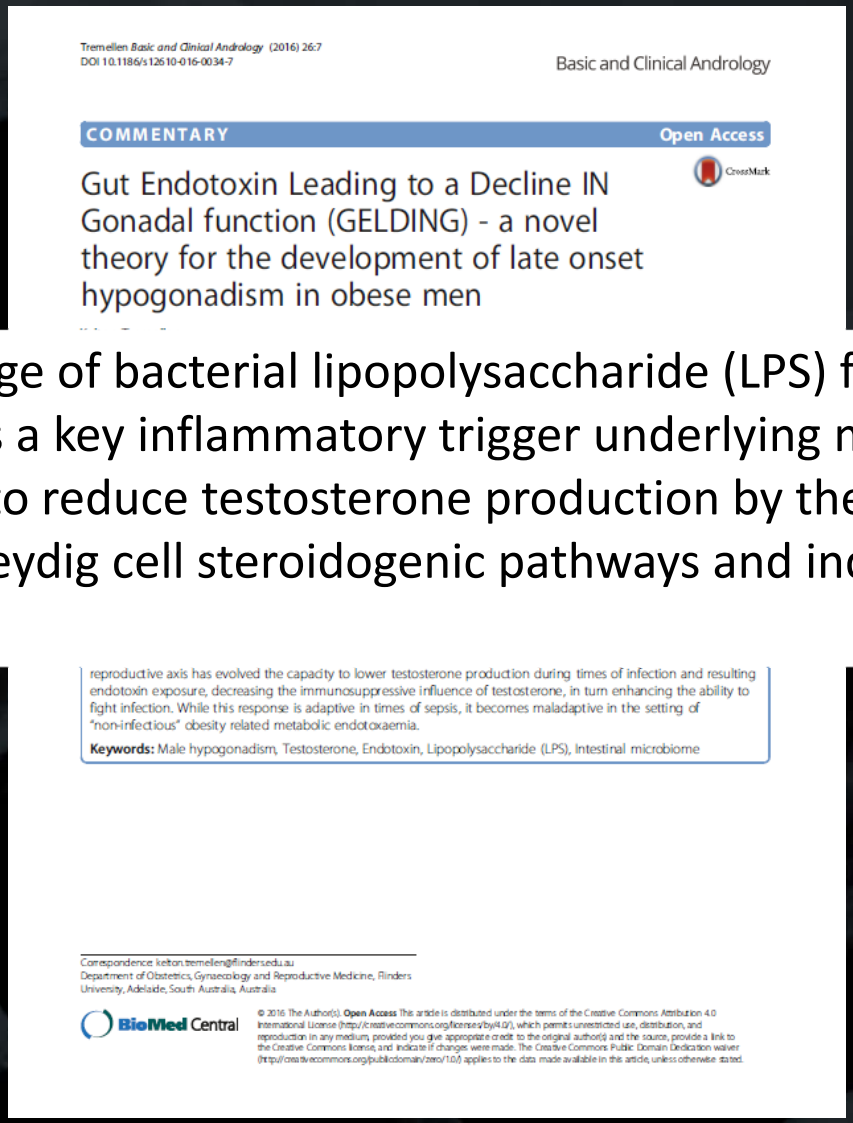

HIGHER ORDER
HEALTH

OVERVIEW

1. It’s about balance
2. Where’s the problem?
3. Gut health and hormones
4. Chemical toxins and hormones
5. Can we have sick fat cells?
6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

HIGHER ORDER HEALTH


Gut Function and Hormones
HIGHER ORDER
HEALTH



Tremellen *Basic and Clinical Andrology* (2016) 26:7
DOI 10.1186/s12610-016-0034-7

Basic and Clinical Andrology

COMMENTARY Open Access

Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING) - a novel theory for the development of late onset hypogonadism in obese men

Trans-mucosal passage of bacterial lipopolysaccharide (LPS) from the gut lumen into the circulation is a key inflammatory trigger underlying male hypogonadism. Endotoxin is known to reduce testosterone production by the testis, both by direct inhibition of Leydig cell steroidogenic pathways and indirectly by reducing pituitary LH drive.

reproductive axis has evolved the capacity to lower testosterone production during times of infection and resulting endotoxin exposure, decreasing the immunosuppressive influence of testosterone, in turn enhancing the ability to fight infection. While this response is adaptive in times of sepsis, it becomes maladaptive in the setting of "non-infectious" obesity related metabolic endotoxaemia.

Keywords: Male hypogonadism, Testosterone, Endotoxin, Lipopolysaccharide (LPS), Intestinal microbiome

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HIGHER ORDER HEALTH

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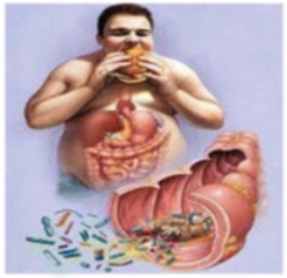
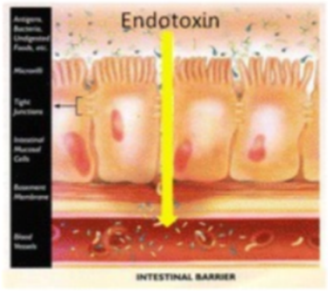
COMMENTARY Open Access

Gut Endotoxin Leading to a Decline IN

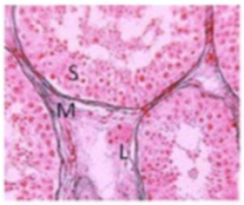


A **high fat/ calorie diet** alters the gut microbiome, leading to a breakdown in the mucosal barrier and the passage of endotoxin from the gut into the circulation - so called **metabolic endotoxaemia**

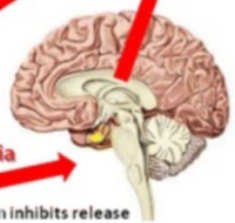


Exposure of the testis to endotoxin activates interstitial macrophages (M) which inhibit steroidogenic enzymes in Leydig cells (L) and creates oxidative stress- **all lowering testosterone production**

Reduced intra-testicular levels of Testosterone and oxidative stress impair spermatogenesis in the seminiferous tubules (S)- reduction in sperm quality



Diminished LH drive for testosterone production



Metabolic Endotoxaemia

Endotoxin inhibits release of LH from the pituitary

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informa healthcare

ORIGINAL ARTICLE

Metabolic endotoxaemia – a potential novel link between ovarian inflammation and impaired progesterone production

Kelton Tremellen[1,2], Naeema Syedi[2], Sze Tan[2], and Karma Pearce[2]

[1]Repromed, Dulwich, South Australia, and [2]School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Adelaide, South Australia

Endotoxemia (LPS) was negatively correlated with progesterone. The observed correlations, together with previously published animal studies linking endotoxin exposure to impaired luteal function, suggest that the translocation of bacterial endotoxin from the gut lumen into the circulation has the potential to interfere with progesterone production and result in luteal deficiency.

cycle, fecundity and maintenance of pregnancy [1]. Epidemiological studies have identified that obesity and several different forms of bowel disease (Inflammatory Bowel Disease, Irritable Bowel Syndrome and Coeliac Disease) are associated with menstrual irregularity due to impaired ovarian steroid hormone production [2–4]. Despite these conditions having widely varying pathologies, they all have one thing in common-the presence of a "leaky gut" wall with resulting translocation of bacterial endotoxin from the gut lumen into the systemic circulation [5–9]. Extensive evidence from animal studies suggests that inflammation triggered by exposure to bacterial endotoxin, either through infection [10–13], or experimental administration of endotoxin [14–17], has the potential to impair corpus luteum function, reducing estrogen and progesterone production. Furthermore, the *in vitro* application of LPS to rodent and bovine granulosa cell cultures has been reported to up-regulate their production of inflammatory cytokines such as IL-6 [18–20], which in turn reduces their production of estrogen and progesterone [21,22].

As such, the primary aim of this pilot "proof of concept" study was to determine if systemic endotoxin exposure (endotoxaemia) results in an inflammatory response within the ovary (follicular fluid IL-6), and therefore in principal can interfere with ovarian function. Secondly, we wished to analyse if endotoxaemia

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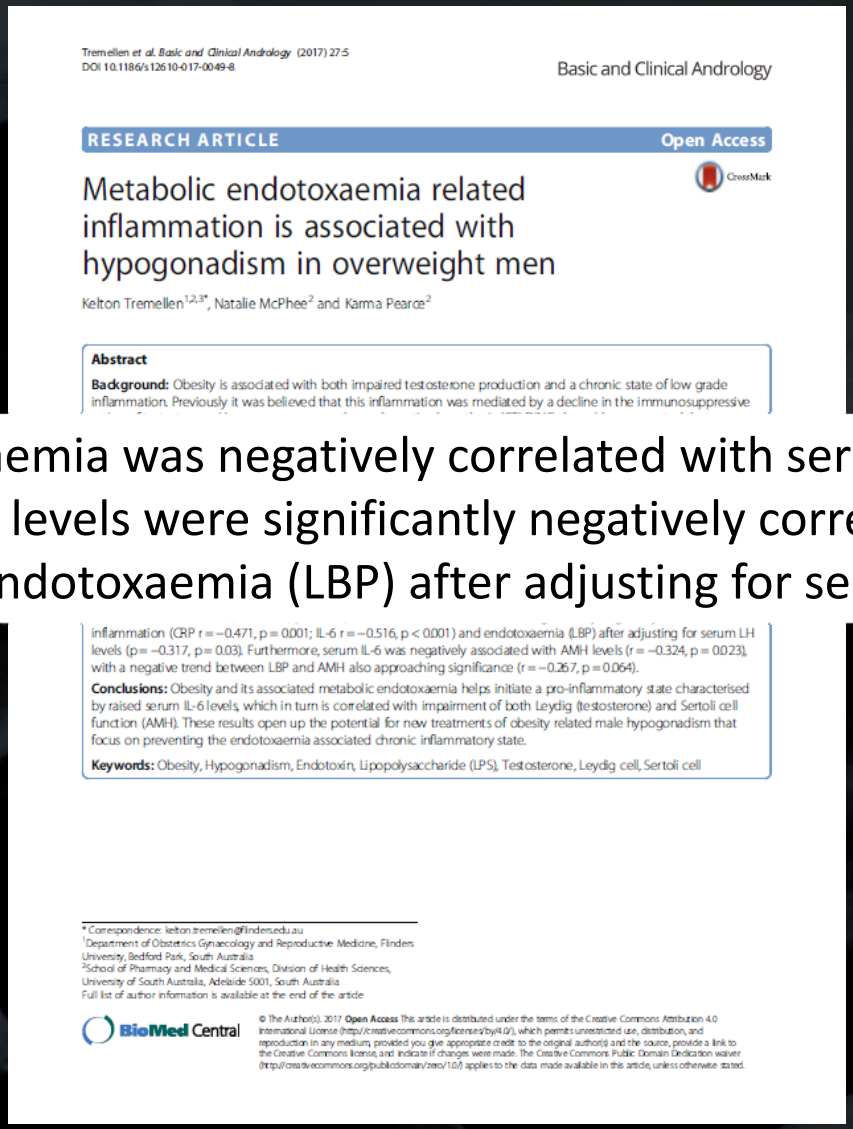
Between December 2012 and April 2013 we enrolled 45 women undergoing infertility treatment at a private reproductive medicine unit (Repromed, Adelaide, South Australia). All participants underwent a GnRH antagonist cycle of IVF using recombinant FSH (Gonal F, Merck Serono, Frenches Forrest, Australia; Puregon, MSD, South Granville, Australia) controlled ovarian hyperstimulation, with final oocyte maturation induced by subcutaneous injection of recombinant hCG (250 µg, Ovidrel, Merck Serono, Frenches Forrest, Australia), before an oocyte retrieval was performed 36 h later under sedation. Patients who had a medical diagnosis of an autoimmune disease, or who were on any immunosuppressive medication were excluded from the study. Participants were only enrolled once in the study (no repeat cycles).

A serum sample for assessment of reproductive hormones and a plasma sample for analysing inflammatory markers were taken immediately before induction of anaesthesia. Serum estrogen, progesterone and testosterone were analysed using an automated chemo-luminescent assay (ADVIA Centaur system, Siemens, Bayswater, Australia), while serum Anti-Mullerian Hormone (AMH) was analysed by ELISA (Immunotech, Beckman-Coulter, Marseille, France). A sample of follicular fluid was collected from the first mature size ovarian follicle, frozen at – 70 degrees Celsius and later assessed for steroid hormones (progesterone, estrogen) and IL-6 concentration by ELISA (R & D Systems, Minneapolis, MN, USA).



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DOI 10.1186/s12610-017-0049-8

Basic and Clinical Andrology

RESEARCH ARTICLE Open Access

Metabolic endotoxaemia related inflammation is associated with hypogonadism in overweight men

Kelton Tremellen[1,2,3*], Natalie McPhee[2] and Karma Pearce[2]

Abstract

Background: Obesity is associated with both impaired testosterone production and a chronic state of low grade inflammation. Previously it was believed that this inflammation was mediated by a decline in the immunosuppressive

inflammation (CRP r = −0.471, p = 0.001; IL-6 r = −0.516, p < 0.001) and endotoxaemia (LBP) after adjusting for serum LH levels (p = −0.317, p = 0.03). Furthermore, serum IL-6 was negatively associated with AMH levels (r = −0.324, p = 0.023), with a negative trend between LBP and AMH also approaching significance (r = −0.267, p = 0.064).

Conclusions: Obesity and its associated metabolic endotoxaemia helps initiate a pro-inflammatory state characterised by raised serum IL-6 levels, which in turn is correlated with impairment of both Leydig (testosterone) and Sertoli cell function (AMH). These results open up the potential for new treatments of obesity related male hypogonadism that focus on preventing the endotoxaemia associated chronic inflammatory state.

Keywords: Obesity, Hypogonadism, Endotoxin, Lipopolysaccharide (LPS), Testosterone, Leydig cell, Sertoli cell

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Full list of author information is available at the end of the article

Metabolic endotoxaemia was negatively correlated with serum testosterone. Serum testosterone levels were significantly negatively correlated with inflammation and endotoxaemia (LBP) after adjusting for serum LH levels.

HIGHER ORDER HEALTH

Endotoxin tolerance of adrenal gland: Attenuation of corticosterone production in response to lipopolysaccharide and adrenocorticotropic hormone*

Shujuan Liu, MSc; Xiaoyan Zhu, MD, PhD; Yujian Liu, MD, PhD; Changnan Wang, BSc; Shan Wang, BSc; Xiaolu Tang, MD, MSc; Xin Ni, MD, PhD

Objectives: **Reversible adrenal insufficiency frequently has been diagnosed in critically ill patients with sepsis who have either low basal cortisol levels or low cortisol responses to adrenocorticotropic hormone (ACTH) stimulation. It is generally accepted that a phenomenon called "endotoxin tolerance" contributes to immunosuppression during sepsis. The present study was to investigate whether endotoxin tolerance occurs in the**

Measurements and Main Results: **Toll-like receptor 4 was expressed in adrenal gland and primary fasciculata-reticularis cells. Plasma corticosterone response to ACTH was decreased in rats receiving preinjection of lipopolysaccharide. Lipopolysaccharide pretreatment caused a significant decrease in corticosterone production in response to subsequent ACTH and lipopolysaccharide stimulation in primary fasciculata-reticularis cells. Lipopolysaccharide pretreat-**

Reversible adrenal insufficiency frequently has been diagnosed in critically ill patients with sepsis who have either low basal cortisol levels or low cortisol responses to adrenocorticotropic hormone (ACTH) stimulation. It is generally accepted that a phenomenon called "endotoxin tolerance" contributes to immunosuppression during sepsis.

vere infectious diseases such as sepsis, physical stressors and inflammatory responses strongly activate the HPA axis and stimulate the release of adrenocorticotropic hormone (ACTH), which in turn stimulates the secretion of glucocorticoids (GCs) from the adrenal cortex (1, 2).

system (3, 4). However, reversible adrenal insufficiency has frequently been diagnosed in critically ill patients with sepsis who have either low basal cortisol levels or low cortisol responses to ACTH stimulation (5–7). Furthermore, corticosteroid insufficiency is always associated

Gram-negative bacteria accounts for approximately one-half of all serious human infections and sepsis (10). Endotoxin (lipopolysaccharide [LPS]), a major component of the outer membrane of Gram-negative bacteria, is responsible for most pathophysiological phenomena associated with Gram-negative infections (11, 12). Many studies have shown that administration of LPS can activate HPA and result in increases in circulating corticosteroid *in vivo* (13). However, the mechanisms through which LPS stimulates the HPA axis and the exact site of its action within the HPA axis are still unclear. Although previous studies have shown that LPS exerts this effect principally by stimulating corticotropin-releasing hormone secretion (14–16), there is

*See also p. 597.

From the Department of Physiology (SL, XZ, CW, SW, XT, XN), Department of Pathophysiology (YL), and The Key Laboratory of Molecular Neurobiology of Ministry of Education (SL, XZ, CW, SW, XT, XN), Second Military Medical University, Shanghai, People's Republic of China.

Supported, in part, by National Natural Science Foundation of China (30770846 and 30670815) and Science and Technology Commission of Shanghai Municipals (09XD1405600).

SL and XZ contributed equally to this work.

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The authors have not disclosed any potential conflicts of interest.

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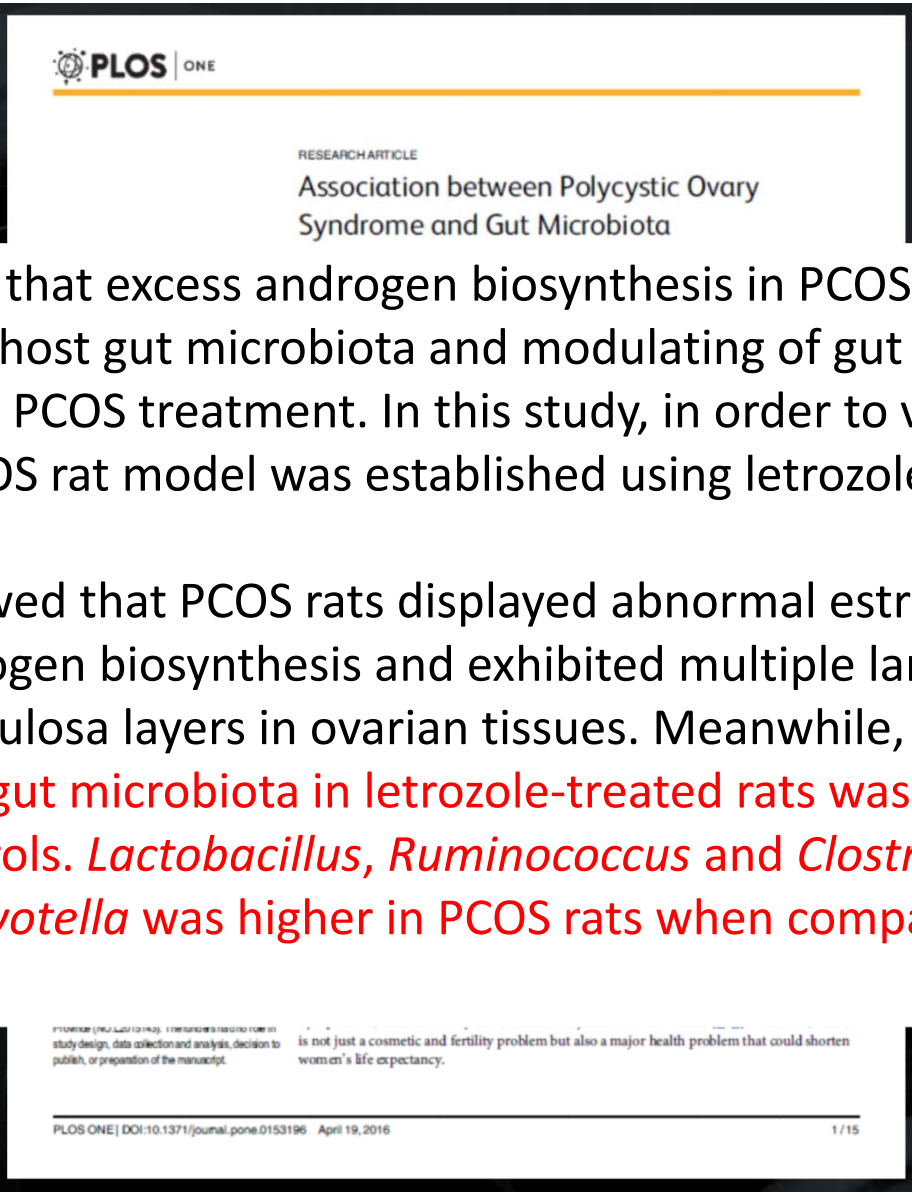


PLOS | ONE

RESEARCH ARTICLE

Association between Polycystic Ovary Syndrome and Gut Microbiota

We hypothesize that excess androgen biosynthesis in PCOS may result in the dysbiosis of host gut microbiota and modulating of gut microbiota may be beneficial for PCOS treatment. In this study, in order to verify our hypotheses, PCOS rat model was established using letrozole induction.

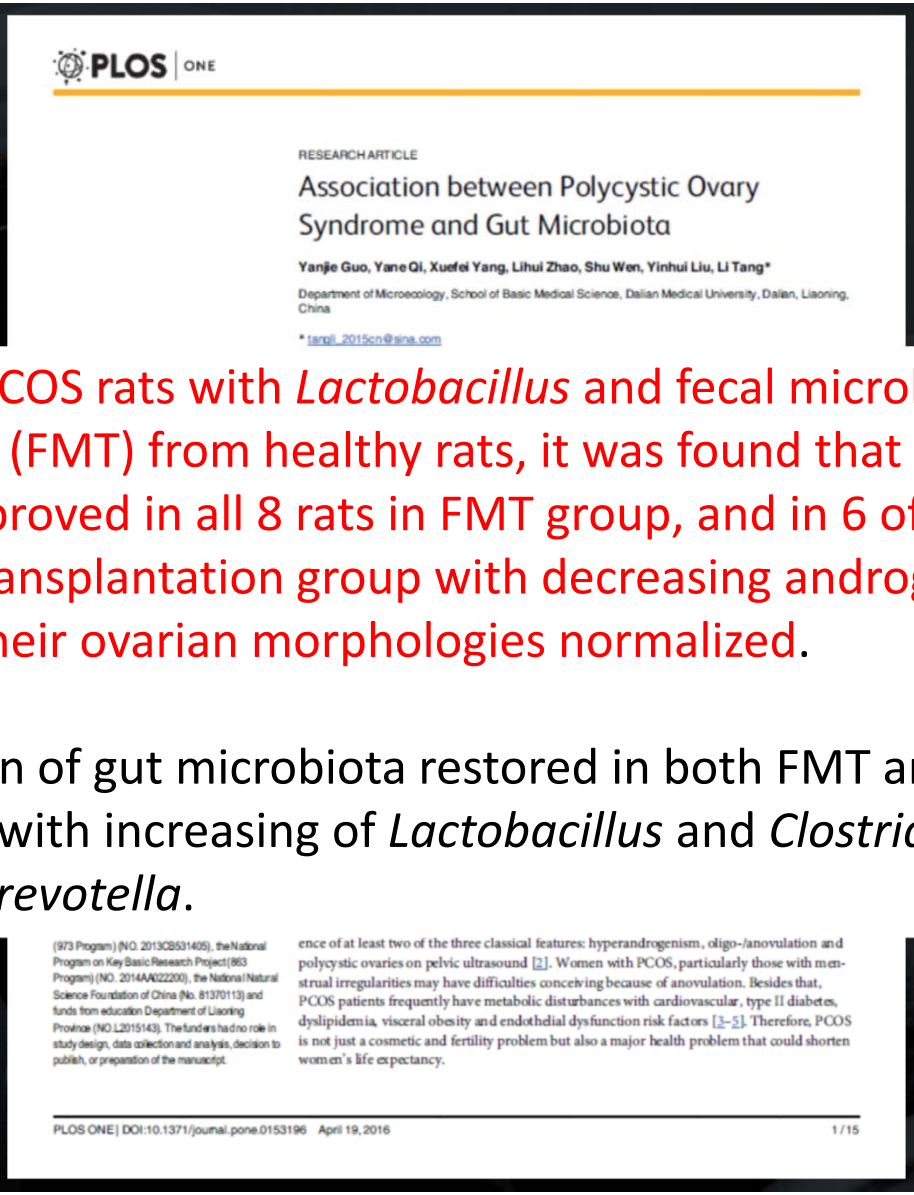
The results showed that PCOS rats displayed abnormal estrous cycles with increasing androgen biosynthesis and exhibited multiple large cysts with diminished granulosa layers in ovarian tissues. Meanwhile, the composition of gut microbiota in letrozole-treated rats was different from that in the controls. *Lactobacillus*, *Ruminococcus* and *Clostridium* were lower while *Prevotella* was higher in PCOS rats when compared with control rats.

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

is not just a cosmetic and fertility problem but also a major health problem that could shorten women's life expectancy.

PLOS ONE | DOI:10.1371/journal.pone.0153196 April 19, 2016 1 / 15

HIGHER ORDER HEALTH



PLOS | ONE

RESEARCH ARTICLE

Association between Polycystic Ovary Syndrome and Gut Microbiota

Yanjie Guo, Yane Qi, Xuefei Yang, Lihui Zhao, Shu Wen, Yinhui Liu, Li Tang*

Department of Microecology, School of Basic Medical Science, Dalian Medical University, Dalian, Liaoning, China

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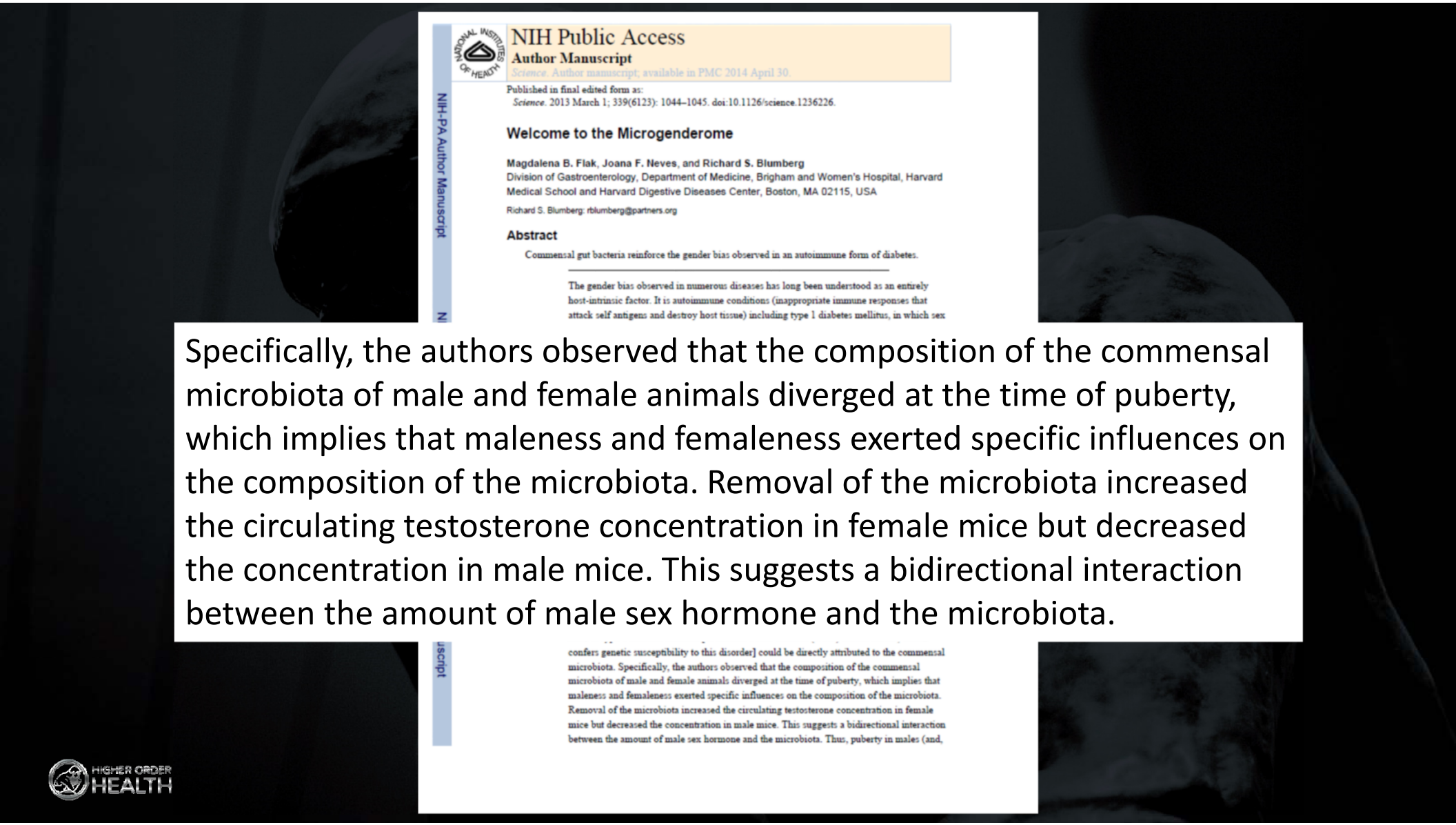
After treating PCOS rats with *Lactobacillus* and fecal microbiota transplantation (FMT) from healthy rats, it was found that the estrous cycles were improved in all 8 rats in FMT group, and in 6 of the 8 rats in *Lactobacillus* transplantation group with decreasing androgen biosynthesis. Their ovarian morphologies normalized.

The composition of gut microbiota restored in both FMT and *Lactobacillus* treated groups with increasing of *Lactobacillus* and *Clostridium*, and decreasing of *Prevotella*.

(973 Program) (NO. 2013CB531405), the National Program on Key Basic Research Project (863 Program) (NO. 2014AA022200), the National Natural Science Foundation of China (No. 81370113) and funds from education Department of Liaoning Province (NO.L2015143). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ence of at least two of the three classical features: hyperandrogenism, oligo-/anovulation and polycystic ovaries on pelvic ultrasound [2]. Women with PCOS, particularly those with menstrual irregularities may have difficulties conceiving because of anovulation. Besides that, PCOS patients frequently have metabolic disturbances with cardiovascular, type II diabetes, dyslipidemia, visceral obesity and endothelial dysfunction risk factors [3–5]. Therefore, PCOS is not just a cosmetic and fertility problem but also a major health problem that could shorten women's life expectancy.



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Welcome to the Microgenderome

Magdalena B. Flak, **Joana F. Neves**, and **Richard S. Blumberg**
Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School and Harvard Digestive Diseases Center, Boston, MA 02115, USA

Richard S. Blumberg: rblumberg@partners.org

Abstract

Commensal gut bacteria reinforce the gender bias observed in an autoimmune form of diabetes.

The gender bias observed in numerous diseases has long been understood as an entirely host-intrinsic factor. It is autoimmune conditions (inappropriate immune responses that attack self antigens and destroy host tissue) including type 1 diabetes mellitus, in which sex

Specifically, the authors observed that the composition of the commensal microbiota of male and female animals diverged at the time of puberty, which implies that maleness and femaleness exerted specific influences on the composition of the microbiota. Removal of the microbiota increased the circulating testosterone concentration in female mice but decreased the concentration in male mice. This suggests a bidirectional interaction between the amount of male sex hormone and the microbiota.

confers genetic susceptibility to this disorder] could be directly attributed to the commensal microbiota. Specifically, the authors observed that the composition of the commensal microbiota of male and female animals diverged at the time of puberty, which implies that maleness and femaleness exerted specific influences on the composition of the microbiota. Removal of the microbiota increased the circulating testosterone concentration in female mice but decreased the concentration in male mice. This suggests a bidirectional interaction between the amount of male sex hormone and the microbiota. Thus, puberty in males (and,

HIGHER ORDER HEALTH


HIGHER ORDER
HEALTH

OVERVIEW

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HIGHER ORDER HEALTH

Chemical Toxins and Hormones

HIGHER ORDER HEALTH

Table 2
Chemicals Acting at Cholesterol Transport to Mitochondria

Sites of action	*Chemical*	*Use*
Cholesterol transport	Econazole	Antifungal
	Miconazole	Antifungal
	Phthalates	Plasticizer
	TCDD	Agricultural and industrial chemical
StAR	Cadmium	Metal
	Dimethoate	Insecticide
	Econazole	Antifungal
	Hexachlorocyclohexanes, lindane	Pesticide
	Lead	Metal
	Miconazole	Antifungal
Mitochondrial integrity	Surfactants	Agricultural and industrial chemical
PBR	PFDA	Plasticizer, surfactant
	Phthalates	Plasticizer

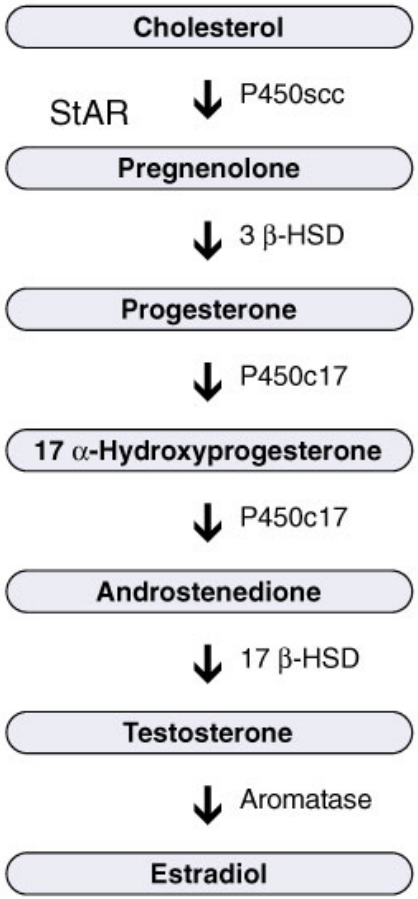
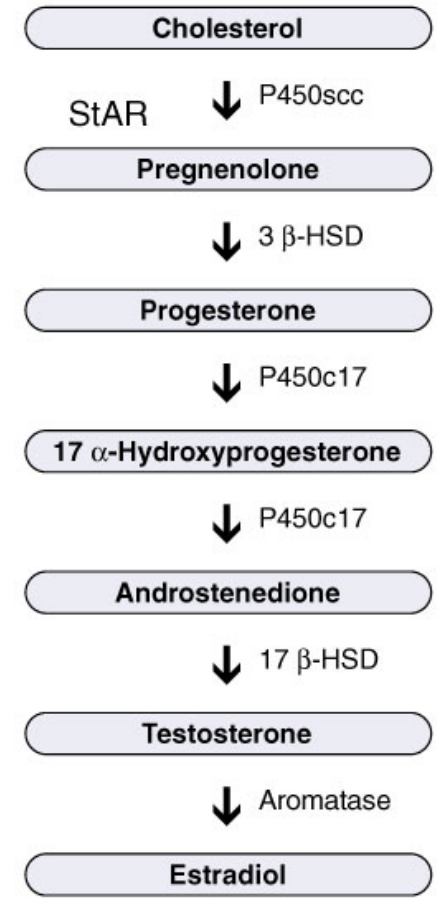
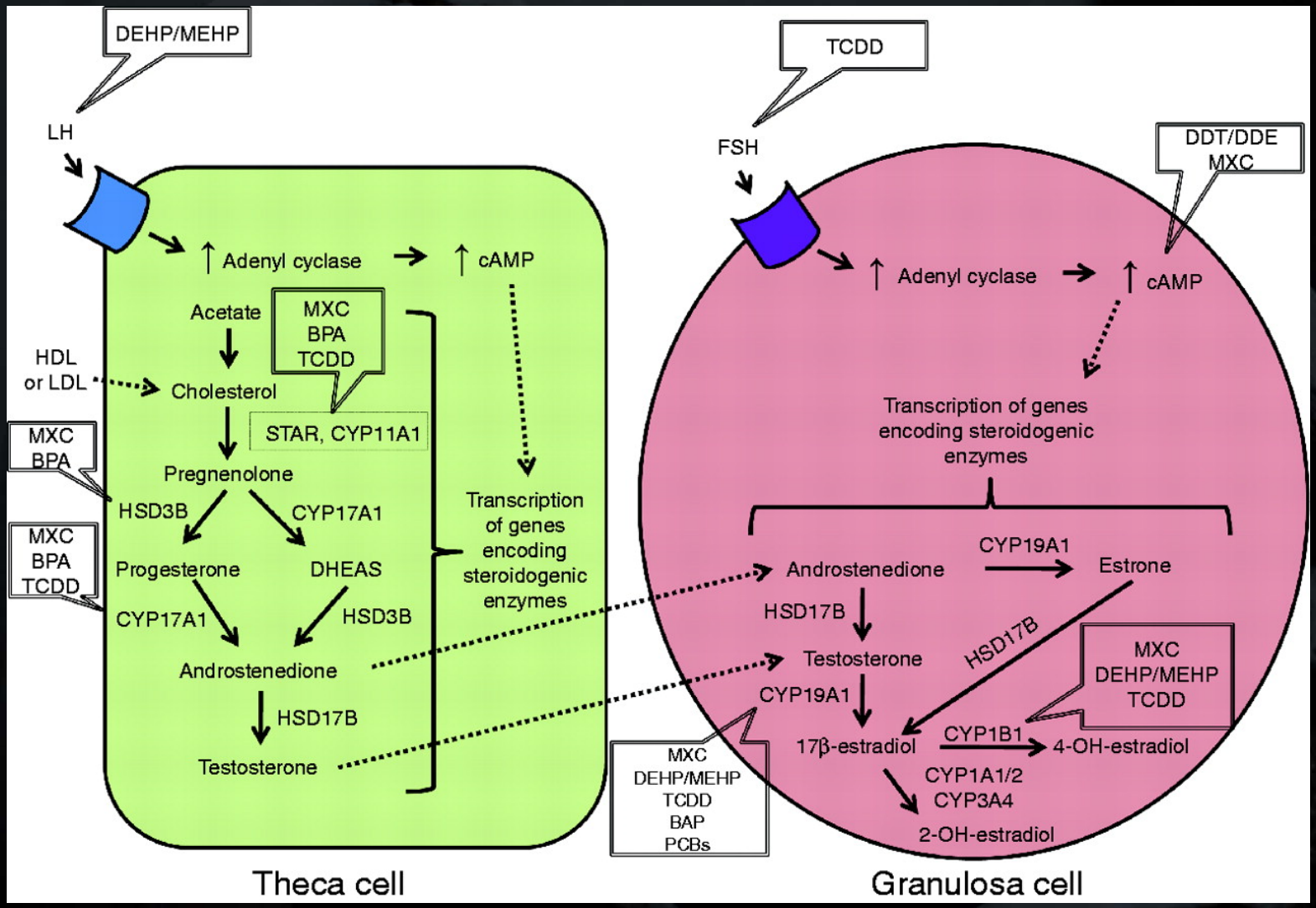


Table 3
Chemicals Acting at Steroidogenic Enzyme Activity and/or Expression

Sites of action	*Chemical*	*Use*
CYP11A1	Dimethoate	Insecticide
	Lead	Metal
	Methoxychlor and metabolite	Insecticide
	PCB	Agricultural and industrial chemical
	Phthalates	Plasticizer
	TCDD	Agricultural and industrial chemical
3β-HSD	Arsenic	Metal
	Cadmium	Metal
	Chromium	Metal
	Hexachlorocyclohexanes, lindane	Pesticide
	Ketoconazole	Antifungal
	Lead	Metal
	Mercury	Metal
	PCB	Agricultural and industrial chemical
	Phthalates	Plasticizer
	Tributyltin, triphenyltin	Biocide
CYP17	Bisphenol A	Plasticizer
	Interferon	Antiviral
	Ketoconazole	Antifungal
	PCB	Agricultural and industrial chemical
	Phthalates	Plasticizer
	TCDD	Agricultural and industrial chemical
	Tributyltin, triphenyltin	Biocide
17β-HSD	Arsenic	Metal
	Cadmium	Metal
	Dicofol	Miticide
	Hexachlorocyclohexanes, lindane	Pesticide
	Ketoconazole	Antifungal
	PCB	Agricultural and industrial chemical
	Tributyltin, triphenyltin	Biocide




DEHP/MEHP
LH
↑ Adenyl cyclase
↑ cAMP
Acetate
MXC
BPA
TCDD
HDL
or LDL
Cholesterol
STAR, CYP11A1
MXC
BPA
Pregnenolone
HSD3B
CYP17A1
MXC
BPA
TCDD
Progesterone
DHEAS
CYP17A1
HSD3B
Androstenedione
HSD17B
Testosterone
Transcription
of genes
encoding
steroidogenic
enzymes
TCDD
FSH
DDT/DDE
MXC
↑ Adenyl cyclase
↑ cAMP
Transcription of genes
encoding steroidogenic
enzymes
CYP19A1
Androstenedione
Estrone
HSD17B
HSD17B
Testosterone
MXC
DEHP/MEHP
TCDD
CYP19A1
17β-estradiol
CYP1B1
4-OH-estradiol
CYP1A1/2
CYP3A4
2-OH-estradiol
MXC
DEHP/MEHP
TCDD
BAP
PCBs
Theca cell
Granulosa cell

Polycystic ovary syndrome and environmental toxins

1. BISPHENOL A → DIRECT EFFECT ON OVARIAN THECA CELLS → Ovary

- ↑ Testosterone
- ↑ mRNA expression: 17ª- hydroxylase, STAR, P450cc

2. BISPHENOL A

- ↓ activity
- 2a hydroxylase Testosterone
- 6a hydroxylase

→ DIRECT EFFECT → Liver

- BPA: A potent SHBG ligand
- ↑ free testosterone
- Disruption of the androgen-to-estrogen balance

3. ANDROGENS

- ↓ UDP-glucuronosyltransferase activity

→ DIRECT EFFECT ON HEPATIC BPA METABOLISM → Liver

- ↓ BPA glucuronidation in liver microsomes
- ↑ Serum levels BPA

Potential BPA interactions with androgen synthesis and metabolism. BPA may directly impact the ovarian theca cells to secrete androgens and additionally can displace T from SHBG, thereby increasing the free androgen index and disrupting the androgen-to-estrogen balance. Androgens decrease hepatic BPA glucuronidation, leading to increased serum free BPA levels and perpetuation of BPA and androgen interactions.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

Roundup as a cause of Adrenal Insufficiency

Doses of 10, 50, 100 and 250 mg/kg bw/d Roundup® were administered for two weeks to adult male rats for two weeks.

At 10 mg/kg bw/d, decrease in cortisol, but seemed to be due to decreased circulating ACTH.

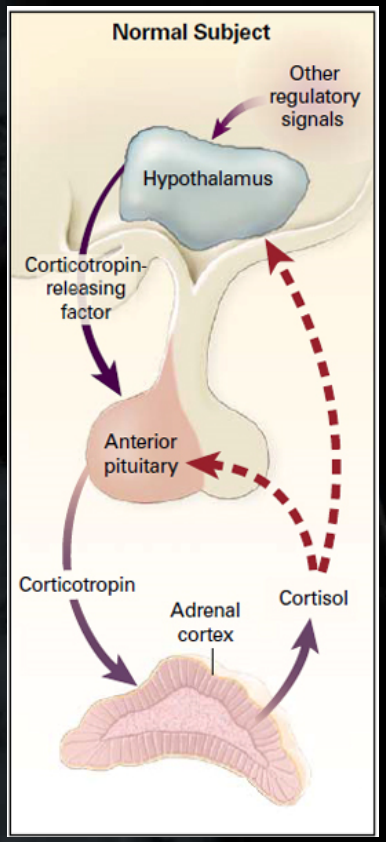
10 mg/kg bw/d is well below the NOAEL for chronic toxicity of glyphosate: 500 mg/kg bw/d for chronic toxicity, according to the US EPA.

Pandey, Aparamita, and Medhamurthy Rudraiah. 2015. "Analysis of Endocrine Disruption Effect of Roundup® in Adrenal Gland of Male Rats." *Toxicology Reports* 2: 1075–85. doi:10.1016/j.toxrep.2015.07.021.

HIGHER ORDER HEALTH

If someone is experiencing hormone symptoms, is it . . .

* Stimulation
* Synthesis
* Release
* Transport
* Conversion
* Receptor binding OR Metabolism and clearance
* Transcription, Translation, Cellular response



HIGHER ORDER HEALTH

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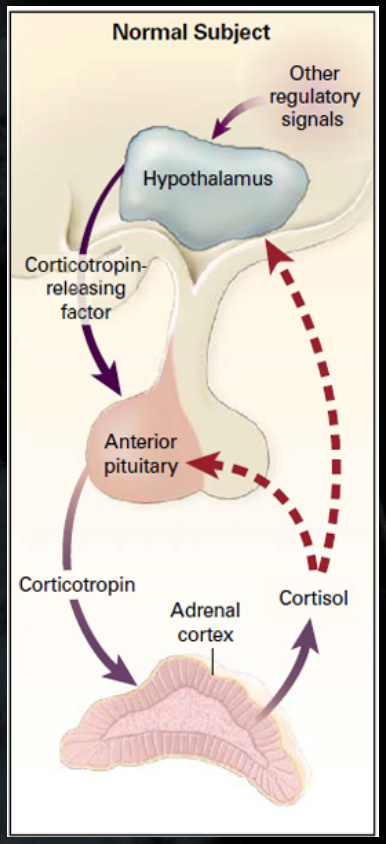
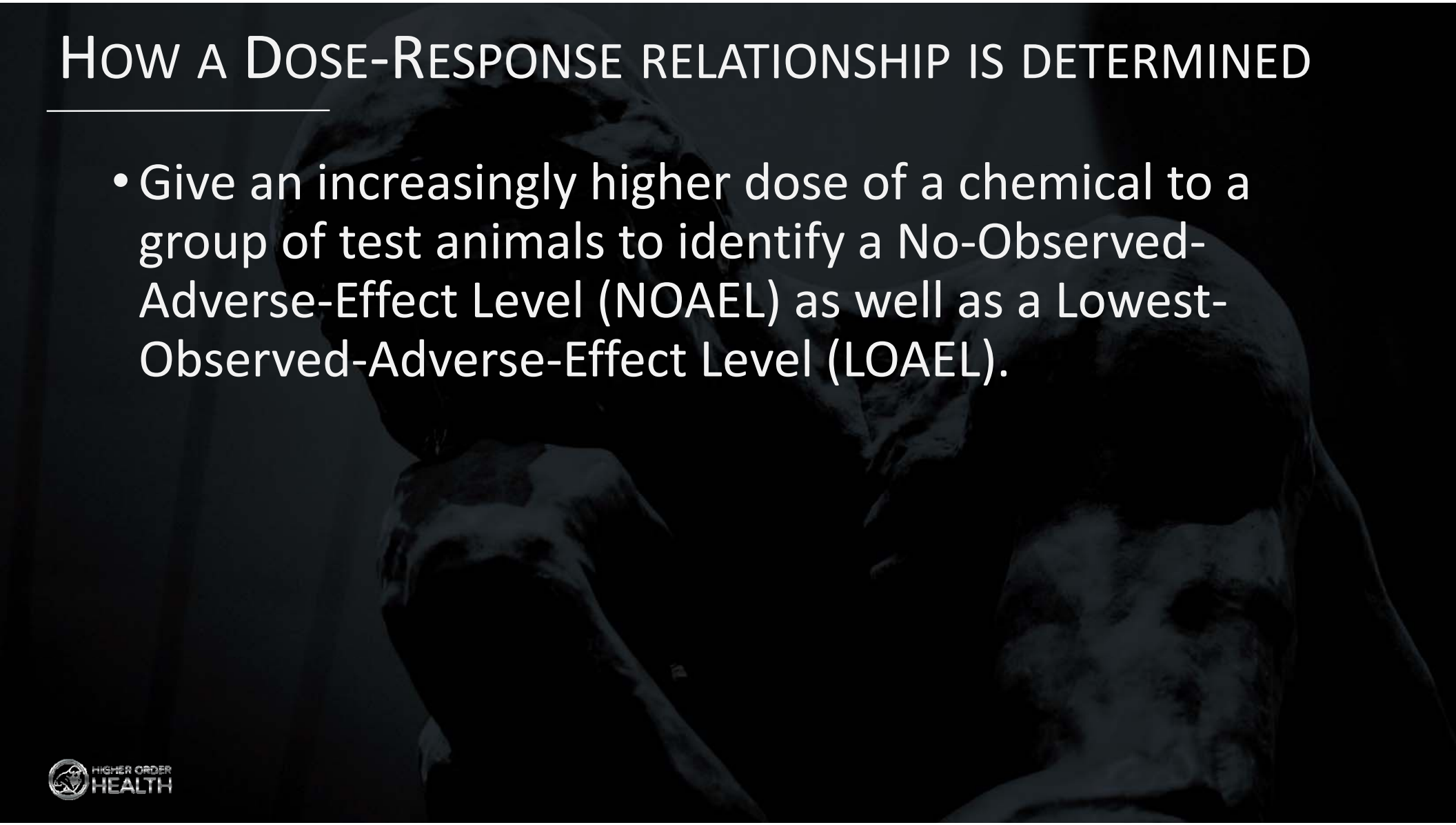


HIGHER ORDER HEALTH

How a Dose-Response relationship is determined

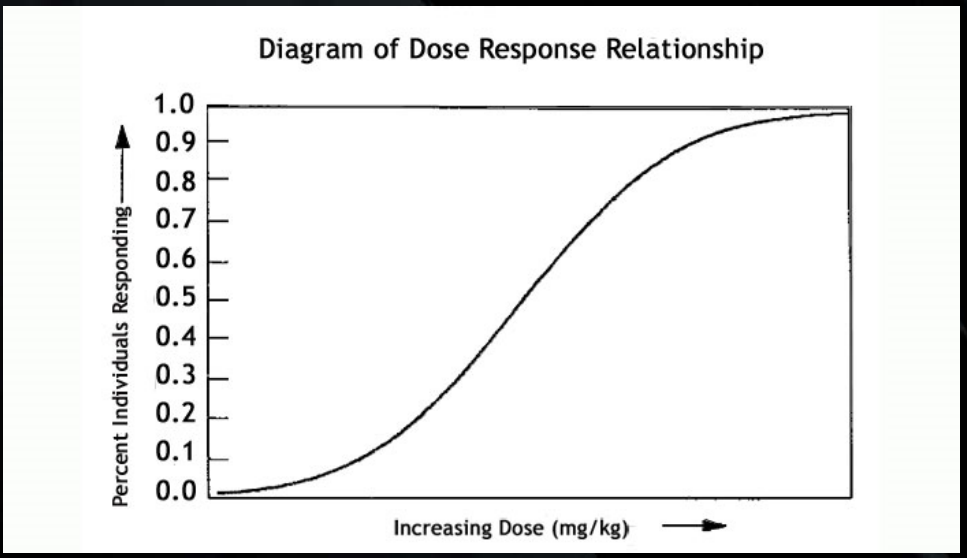
- Give an increasingly higher dose of a chemical to a group of test animals to identify a No-Observed-Adverse-Effect Level (NOAEL) as well as a Lowest-Observed-Adverse-Effect Level (LOAEL).

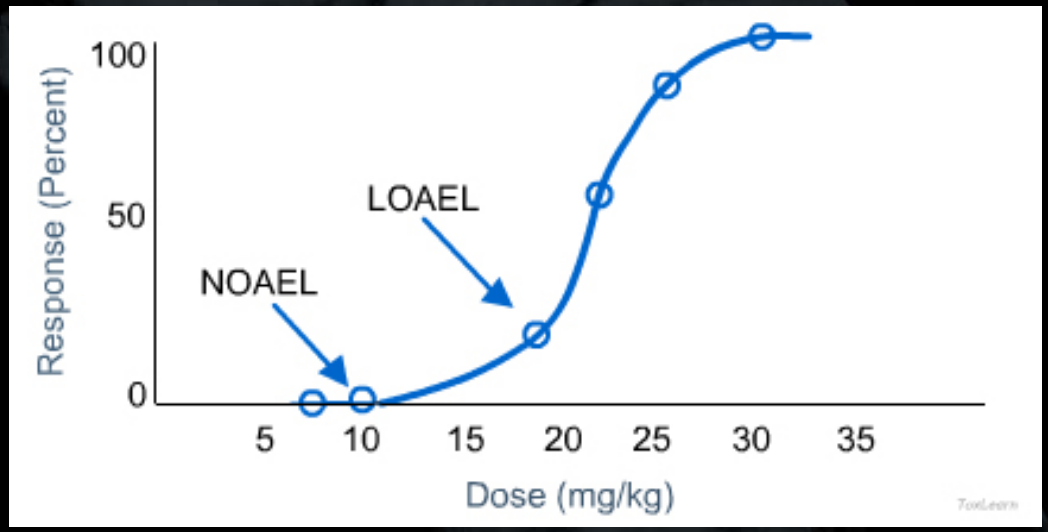


HIGHER ORDER HEALTH

THE DOSE DOESN'T MAKE THE POISON

Dose respons





No observable adverse effect level

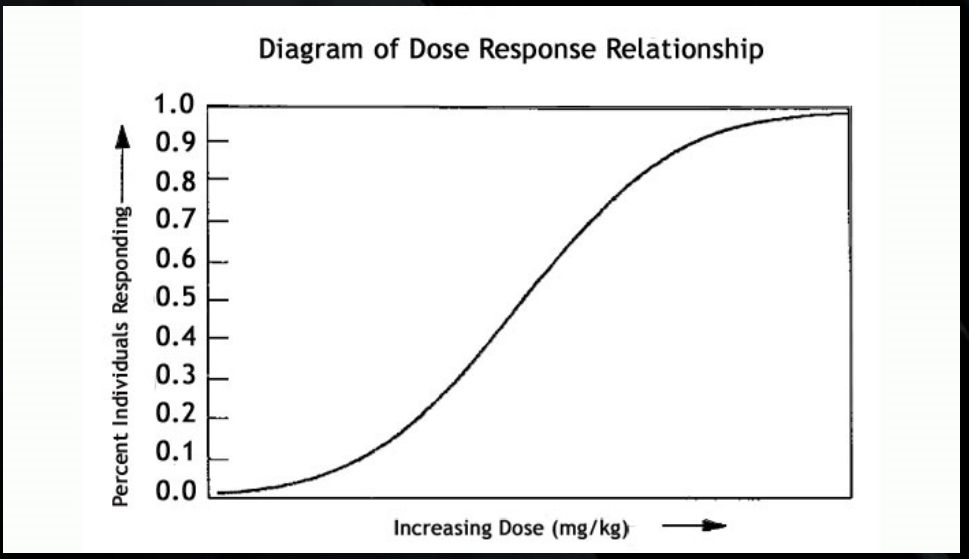
Lowest observable effect level

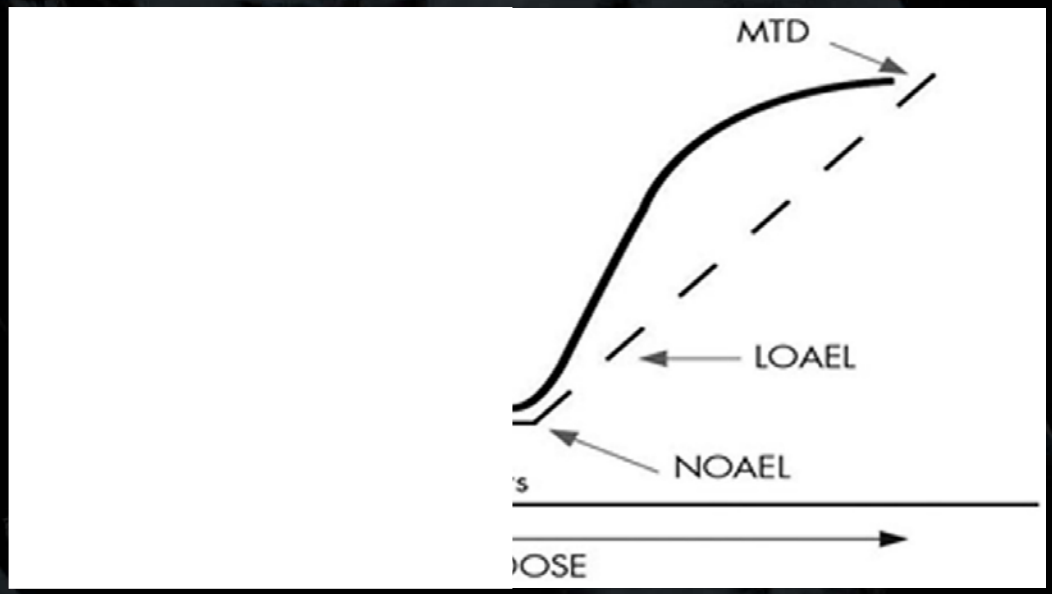
HIGHER ORDER HEALTH

THE DOSE DOESN'T MAKE THE POISON

Dose respons

Non-monotonic dose-response (NMDR)





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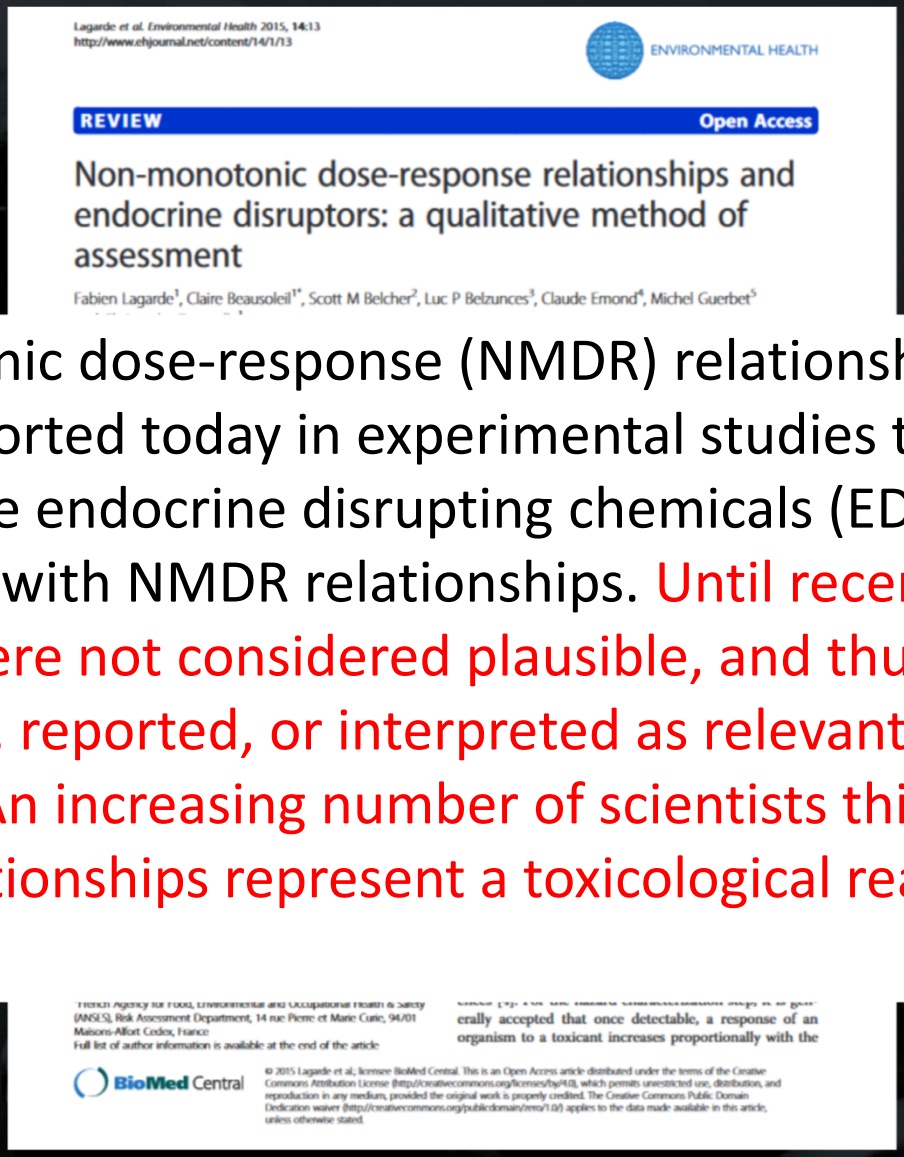

Lagarde et al. Environmental Health 2015, 14:13
http://www.ehjournal.net/content/14/1/13

ENVIRONMENTAL HEALTH

REVIEW Open Access

Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment

Fabien Lagarde[1], Claire Beausoleil[1*], Scott M Belcher[2], Luc P Belzunces[3], Claude Emond[4], Michel Guerbet[5]

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Full list of author information is available at the end of the article

erally accepted that once detectable, a response of an organism to a toxicant increases proportionally with the

BioMed Central

Non-monotonic dose-response (NMDR) relationships are more frequently reported today in experimental studies than they were 10 years ago. The endocrine disrupting chemicals (EDCs) are regularly associated with NMDR relationships. Until recently, NMDR relationships were not considered plausible, and thus they were not published, reported, or interpreted as relevant biological phenomena. An increasing number of scientists think that NMDR relationships represent a toxicological reality.

The Dose DOESN'T Make the Poison

Importantly, our review of the literature finds that NMDRCs are common in the endocrine and EDC literature. In fact, it is plausible that, considering the mechanisms discussed below, NMDRCs are not the exception but should be expected and perhaps even common.

We illustrate that nonmonotonic responses and low-dose effects are remarkably common in studies of natural hormones and EDCs. Whether low doses of EDCs influence certain human disorders is no longer conjecture, because epidemiological studies show that environmental exposures to EDCs are associated with human diseases and disabilities.

Vandenberg, L. N., Colborn, T., Hayes, T. B., Heindel, J. J., Jacobs, D. R., Lee, D.-H., … Myers, J. P. (2012). Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. Endocrine Reviews, 33(3), 378–455.

HIGHER ORDER HEALTH

International Journal of
Environmental Research and Public Health

Review

Endocrine Aspects of Environmental "Obesogen" Pollutants

Francesca Nappi [1,*], Luigi Barrea [1], Carolina Di Somma [2], Maria Cristi Giovanna Muscogiuri [1], Francesco Orio [3] and Silvia Savastano [4]

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Abstract: Growing evidence suggests the causal link between the endo (EDCs) and the global obesity epidemics, in the context in the so-called Dietary intake of contaminated foods and water, especially in associa pattern, and inhalation of airborne pollutants represent the major sources This is of particular concern in view of the potential impact of obesity o diseases, such as type 2 diabetes, cardiovascular disease, and hormon concept is the identification of adipose tissue not only as a preferent but also as an endocrine organ and, as such, susceptible to endocrine exposure to EDCs is critical to the outcome of that exposure, with early l or early postnatal) particularly detrimental because of their permanent e Despite that the mechanisms operating in EDCs effects might vary eno aimed to provide a general overview on the possible association betwe and EDCs, briefly describing the endocrine mechanisms linking EDC of obesity.

Keywords: endocrine-disrupting chemicals; obesity; inflammation; obe

1. Introduction

Global obesity epidemics is most likely due to the interactic causes, that include dysregulation of endocrine and metabolic syste and environmental factors, in the context of the so-called "obesogenic en

Although it has been estimated that the heritability of obesity ra the relative weight of genetic factors and environmental influences might Epigenetics is a potential link between environmental exposures an obligatory and facilitated epigenetic variations could account for the missi Novel molecular approaches evaluating the phenotypic discordance in genome-wide methylation assays, point out that epigenetic changes in operating distinctly for each individual in the pathogenesis of obesity an

Among the "obesogenic" environmental factors, a growing body the exposure to certain environmental pollutants can contribute to the

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Obesogens: an emerging threat to public health

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[2]Department of Pharmaceutical Sciences, University of California, Irvine

Abstract

Endocrine disrupting chemicals (EDCs) are defined as exogenous chemicals, or mi chemicals, that can interfere with any aspect of hormone action. The field of endoc is historically rooted in wildlife biology and reproductive endocrinology where ED demonstrated contributors to infertility, premature puberty, endometriosis, and othe Recently, EDCs have been implicated in metabolic syndrome and obesity. Adipose endocrine organ and, therefore, an organ which is highly susceptible to disturbance subset of EDCs, called "obesogens" promote adiposity by altering programming o development, increasing energy storage in fat tissue, and interfering with neuroend of appetite and satiety. Obesity adds more than $200 billion to U.S. healthcare cost number of obese individuals continues to increase. Hence, there is an urgent, unme understand the mechanisms underlying how exposures to certain EDCs may predis population to be obese. In this review, we discuss the history of obesogen discover origins in reproductive biology to its latest role in the transgenerational inheritance mice. We discuss the development of adipose tissue in an embryo, maintenance of number in adults, how EDC disruption programs stem cells to preferentially make adipocytes, the mechanisms by which chemicals can permanently alter the germlin and whether there are barriers to EDCs in the gametes.

Endocrine disrupting chemicals

The field of endocrine disruption is historically rooted in reproductive e wildlife biology. Endocrine disrupting chemicals (EDCs) are defined as chemicals (including pharmaceuticals), or mixture of chemicals, that ca aspect of hormone action [1]. One poster child EDC, diethylstilbestrol (DE by obstetricians throughout the mid-20th century with the aim of helping pregnancy complications [2]. Regrettably, children born from DES-treated

[3]To whom correspondence should be addressed at blumberg@uci.edu.

Disclosure statement: A.J. has nothing to declare. B.B. is a named inventor on U.S. patents 5,861,274, 6,200, 7,250,273 related to PPARγ.

Curr Obes Rep (2017) 6:18–27
DOI 10.1007/s13679-017-0240-4

ETIOLOGY OF OBESITY (T GILL, SECTION EDITOR)

Endocrine Disruptors and Obesity

Philippa D. Darbre[1]

Published online: 15 February 2017

Abstract
Purpose of Review The purpose of this review was to summarise current evidence that some environmental chemicals may be able to interfere in the endocrine regulation of energy metabolism and adipose tissue structure.
Recent Findings Recent findings demonstrate that such endocrine-disrupting chemicals, termed "obesogens", can promote adipogenesis and cause weight gain. This includes compounds to which the human population is exposed in daily life through their use in pesticides/herbicides, industrial and household products, plastics, detergents, flame retardants and as ingredients in personal care products. Animal models and epidemiological studies have shown that an especially sensitive time for exposure is in utero or the neonatal period.
Summary In summarising the actions of obesogens, it is noteworthy that as their structures are mainly lipophilic, their ability to increase fat deposition has the added consequence of increasing the capacity for their own retention. This has the potential for a vicious spiral not only of increasing obesity but also increasing the retention of other lipophilic pollutant chemicals with an even broader range of adverse actions. This might offer an explanation as to why obesity is an underlying risk factor for so many diseases including cancer.

Keywords Adipogenesis · Bisphenol A · Diethylstilbestrol · Endocrine disruptor · Endocrine-disrupting chemicals · Obesity · Obesogen · Paraben · Peroxisome proliferator-activated receptor · Persistent organic pollutants · Tributyltin

Introduction

The endocrine system plays a fundamental role in regulating the metabolism of fats, carbohydrates and proteins and in ensuring that these fuels provide for the energy needs of the body at all times. Hormones are responsible for storage of excess fuel in times of plenty and mobilisation of fuel in times of need, and most notably in maintaining constant levels of blood glucose. Any alteration to these hormonally driven processes can be expected to lead to an imbalance in metabolism. The main store of energy in the body is provided by fat held in adipocytes in the adipose tissue, and it is now recognised that the adipose tissue is also under endocrine control and can itself act as an endocrine organ capable of secreting hormones [1]. Interference in hormonal control of adipose tissue functions can therefore also lead to inappropriate deposits of fat and, hence, obesity.

Over recent years, many environmental chemicals have been shown to disrupt the actions of hormones and have been termed endocrine-disrupting chemicals (EDCs) or endocrine disruptors [2•]. Although much of the research has focused on disruption of reproduction through interference with steroid hormone actions and on disruption to thyroid hormone action [2•], there are increasing reports that some EDCs can also interfere with regulatory processes in metabolism and in the control of adipocyte function, resulting in imbalances in the regulation of body weight, which can lead to obesity [3•, 4•, 5•]. Such chemicals have been termed "obesogens" [6, 7•].

This article is part of the Topical Collection on *Etiology of Obesity*

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HIGHER ORDER
HEALTH

OVERVIEW

1. It’s about balance
2. Where’s the problem?
3. Gut health and hormones
4. Chemical toxins and hormones
5. Can we have sick fat cells?
6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

HIGHER ORDER HEALTH

Sick Fat Cells

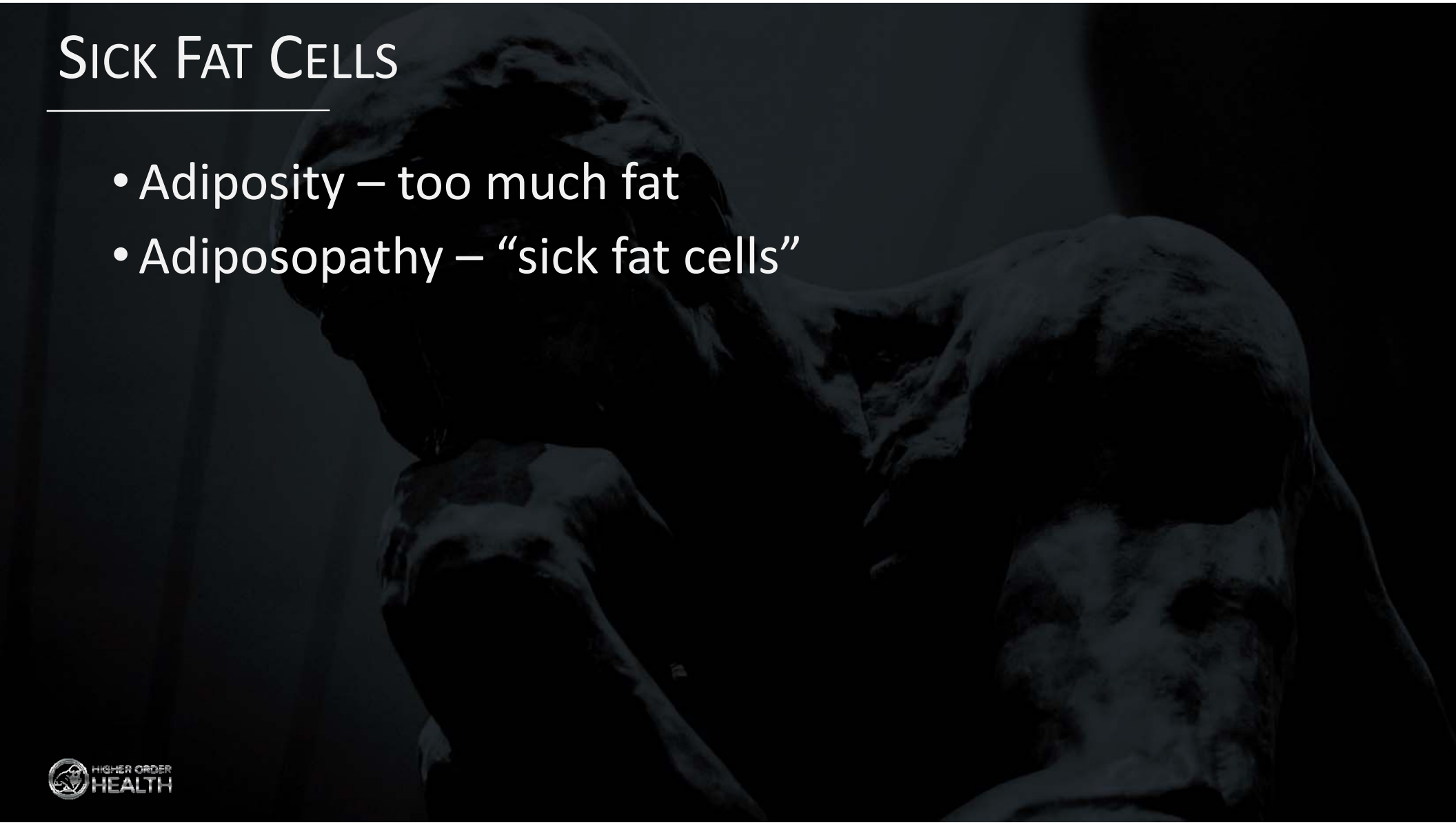
HIGHER ORDER HEALTH

WE'RE TAUGHT . . .

HIGHER ORDER HEALTH

Sick Fat Cells

- Adiposity – too much fat
- Adiposopathy – “sick fat cells”



HIGHER ORDER HEALTH

Proteomics Clin. Appl. 2012, 6, 91–101 DOI 10.1002/prca.201100052

REVIEW

Adipokines: A treasure trove for the discovery of biomarkers for metabolic disorders

Stefan Lehr[1], *Sonja Hartwig*[1] *and Henrike Sell*[2]

[1] Institute of Clinical Biochemistry and Pathobiochemistry, German Diabetes Center, Duesseldorf, Germany
[2] Paul-Langerhans Group, German Diabetes Center, Duesseldorf, Germany

Over 600 “potentially secretory proteins” discovered.
Include: leptin, adiponectin, resistin, IL-6, IL-1B, MCP-1, TNFa, estrogen, testosterone

1 Interorgan crosstalk – a pathophysiological concept in obesity-associated metabolic diseases

Obesity is considered as an epidemic disease with obesity prevalence increasing not only in the Western World but also in developing countries [1]. Imbalanced energy supply and energy consumption coupled with a sedentary lifestyle favor obesity development not only in the adult population but also amongst children [2]. Obesity represents a major risk factor for developing the metabolic syndrome which comprises various metabolic complications such as insulin resistance, type 2 diabetes, non-alcoholic liver disease and cardiovascular diseases [3–6]. For type 2 diabetes, about 80% of diabetes cases can be attributed to weight gain (International Diabetes Federation (2003)), and obesity strongly predisposes to the development of diabetes with a near 100% risk for developing the disease in patients with a BMI >40 [7].

The association between the epidemics of obesity and the metabolic syndrome has promoted research on the endocrine link between expanded adipose tissue, deregulated lipid and glucose homeostasis, vascular dysfunction and other metabolic complications. Organ crosstalk between adipose tissue and organs that are dysfunctional in the obese state has been hypothesized, and a lot of evidence has been collected that this crosstalk exists in various forms. Adipose tissue not only stores energy in the form of triglycerides but it is also a very active endocrine organ releasing proteins and lipids [8, 9]. Proteins released from adipocytes are named adipokines, a definition that has often also been extended to all protein factors released from adipose tissue as a whole [10]. Adipocytes from obese subjects have an altered endocrine function and secretory profile resulting in the increased release of pro-inflammatory adipokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [11].

In a recent and very elegant review [12], several hypotheses on how adipose tissue communicates with other organs in health and disease have been presented in detail. As for the role of free fatty acids (FFA) in this context, it is well known that elevated circulating plasma levels of triglycerides and FFA due to obesity highly contribute to insulin resistance in peripheral tissues such as skeletal muscle [13, 14]. Increased adipose tissue especially in the

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Abbreviations: CM, conditioned medium; **DPP4,** dipeptidyl peptidase 4; **IL-6,** interleukin 6; **MCP,** monocyte chemotactic protein; **PVAT,** perivascular adipose tissue; **TNF-α,** tumor necrosis factor α

HIGHER ORDER HEALTH

doi: 10.1111/j.1742-1241.2008.01848.x

CONSENSUS

International Journal of Clinical Practice

Is adiposopathy (sick fat) an endocrine disease?

Editor's Choice

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Disclosures
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SUMMARY

Objective: To review current consensus and controversy regarding whether obesity is a 'disease', examine the pathogenic potential of adipose tissue to promote metabolic disease and explore the merits of 'adiposopathy' and 'sick fat' as scientifically and clinically useful terms in defining when excessive body fat may represent a 'disease'. **Methods:** A group of clinicians and researchers, all with a background in endocrinology, assembled to evaluate the medical literature, as it pertains to the pathologic and pathogenic potential of adipose tissue, with an emphasis on metabolic diseases that are often promoted by excessive body weight. **Results:** The data support pathogenic adipose tissue as a disease. Challenges exist to convince many clinicians, patients, healthcare entities and the public that excessive body fat is often no less a 'disease' than the pathophysiological consequences related to anatomical abnormalities of other body tissues. 'Adiposopathy' has the potential to scientifically define adipose tissue anatomic and physiologic abnormalities, and their adverse consequences to patient health. Adiposopathy acknowledges that when positive caloric balance leads to adipocyte hypertrophy and visceral adiposity, then this may lead to pathogenic adipose tissue metabolic and immune responses that promote metabolic disease. From a patient perspective, explaining how excessive caloric intake might cause fat to become 'sick' also helps provide a rationale for patients to avoid weight gain. Adiposopathy also better justifies recommendations of weight loss as an effective therapeutic modality to improve metabolic disease in overweight and obese patients. **Conclusion:** Adiposopathy (sick fat) is an endocrine disease.

What's known
Excessive adipose tissue is generally accepted as a "cause" of clinical pathology related to its mass effects, including various cardiovascular, neurologic, pulmonary, musculoskeletal, dermatologic, gastrointestinal, genitourinary, renal, and psychological diseases.

What's new
It is less recognized, and sometimes disputed, that adipocyte hypertrophy and visceral adiposity may contribute ("cause") metabolic diseases such as type 2 diabetes mellitus, hypertension, and dyslipidemia. Adiposopathy and "sick fat" are scientific and clinical terms, respectively, that help define when excessive body fat is a metabolic disease.

Introduction

Obesity is an epidemic (1). An increase in body fat in many individuals and populations directly increases the risk of metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension and dyslipidaemia (2). These are the most common metabolic diseases encountered in endocrine practice, and might also be considered epidemics. However, obesity itself is not yet universally recognised as a disease (3). A sole focus on body mass index (BMI) in attempting to define obesity as a disease is not adequate (4). A more rational approach is to evaluate excessive body fat for its pathogenic potential. This requires recognising that adipose tissue is an active endocrine and immune organ (5), and that pathological disruption of important adipose tissue metabolic processes is detrimental to patient health.

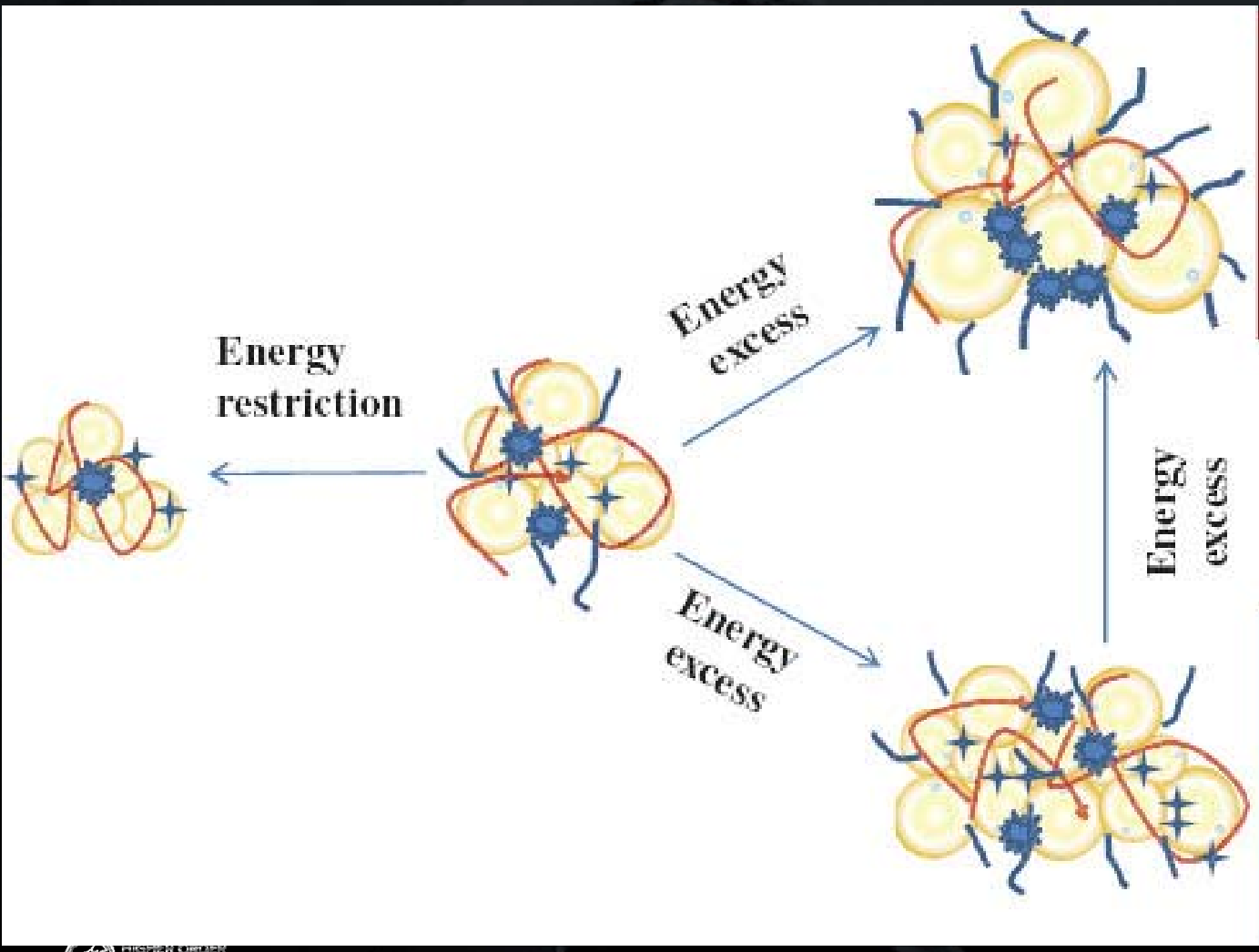
Anatomically, positive caloric balance may lead to adipocyte hypertrophy and visceral adipose tissue accumulation, which are well-known contributors to metabolic disease (3,6). Conversely, weight loss interventions often help correct adipocyte and adipose tissue endocrine and immune abnormalities in overweight patients. This may lead to improvement in multiple metabolic parameters (7), often representing an effective therapy towards treatment of metabolic diseases such as T2DM, hypertension and dyslipidaemia (8).

The failure to adequately recognise the physiologic importance of adipose tissue to metabolic health, both clinically and in the medical/endocrine literature, is significantly because of a failure of existing terminology to adequately describe the pathogenic potential of adipose tissue, and its contribution to metabolic disease. An organ is often considered 'diseased' if it undergoes anatomic abnormalities associated with physiological dysfunction that ultimately lead to unfavourable health consequences. 'Adiposopathy' (adipose-opathy) is a term used to describe

ADIPOSOPATHY

Positive calorie balance, unhealthy diet, sedentary lifestyle:

- Impaired adipogenesis in subcutaneous tissue → growth of adipose beyond vascular supply → inadequate angiogenesis and extracellular matrix → adipocyte hypoxia → ROS → Pathogenic endocrine and immune responses
- Adipocyte hypertrophy → intraorganelle dysfunction → impaired FA storage → increased circulating FFA → visceral adiposity → increased lipotoxicity in organs/tissues

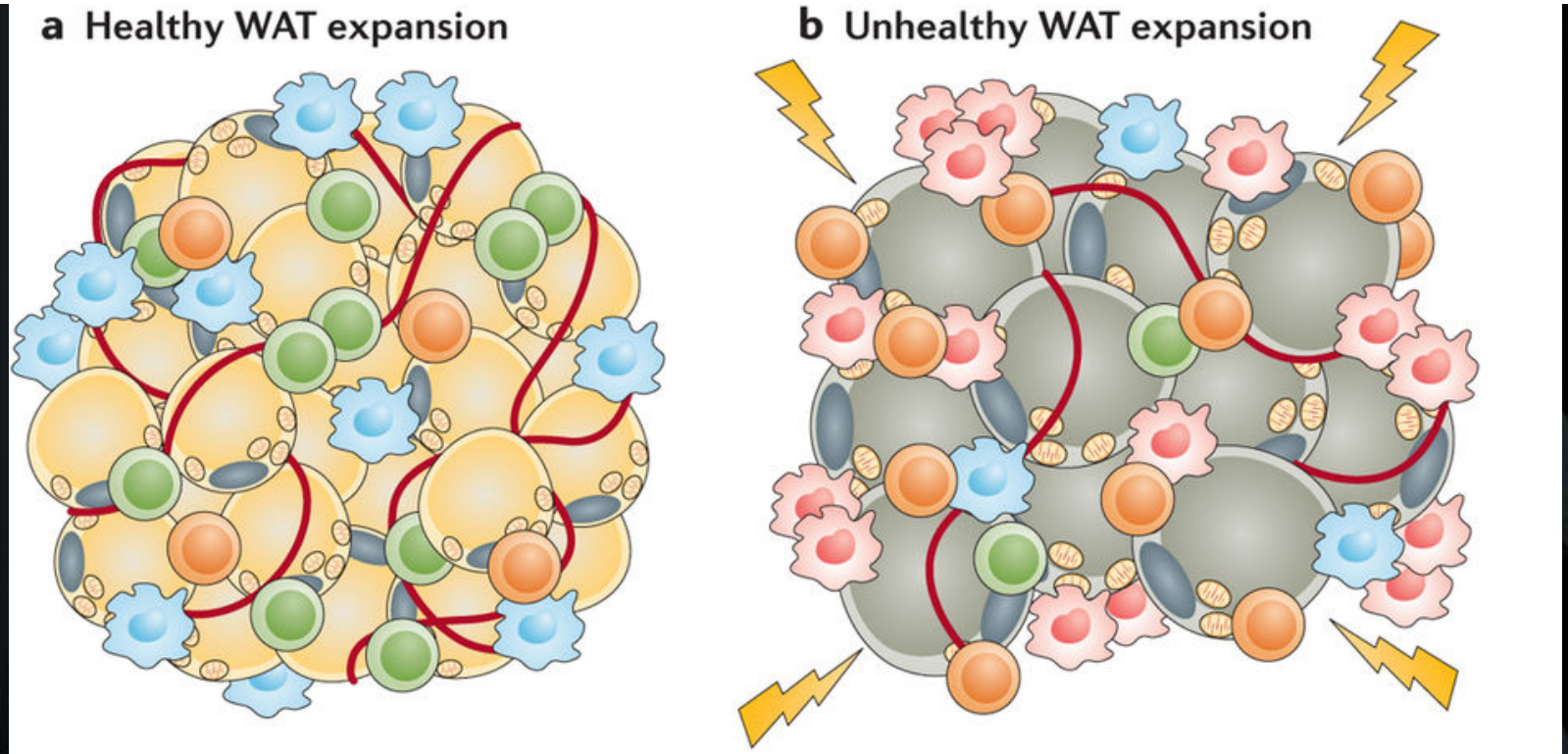


Adipose tissue expansion

- Hypertrophy
- Necrosis
- Hypoxia
- M1 macrophage infiltration
- Fibrosis

Healthy adipose tissue expansion

- Hyperplasia
- M2 macrophage infiltration
- Angiogenesis
- Appropriate ECM remodelling



Nature Reviews | Drug Discovery

Adiposopathy: Treating Pathogenic Adipose Tissue to Reduce Cardiovascular Disease Risk

Harold Bays, MD
Helena W. Rodbard, MD
Alan Bruce Schorr, DO

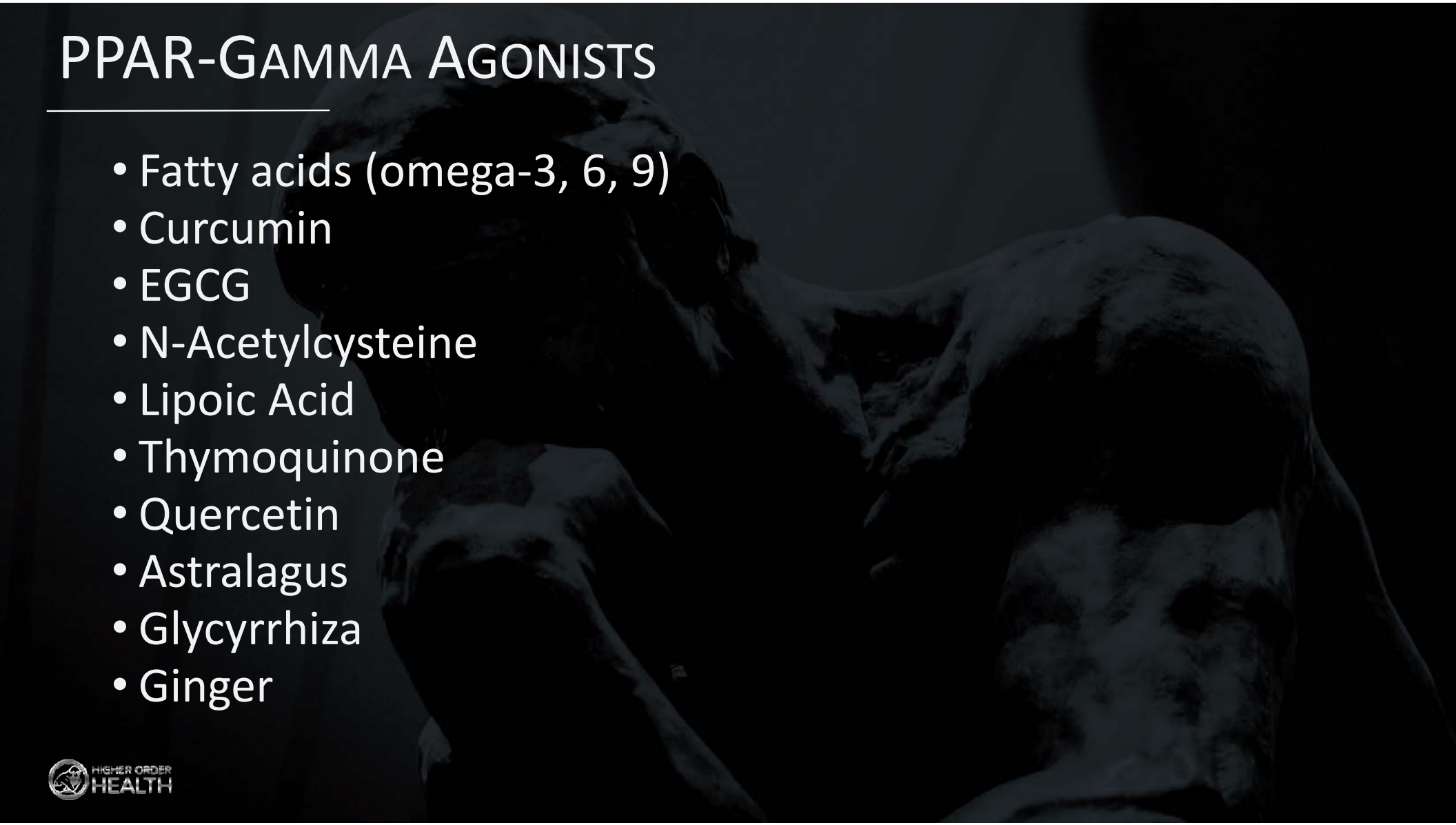
Weight loss through improved nutrition and increased physical activity, improves adiposopathy and improves many metabolic diseases whose prevalence are directly associated with an increase in body fat and sedentary lifestyle. Cannabinoid receptor antagonists improve adiposopathy through weight reduction and favorable metabolic effects upon multiple body organs (including adipocytes). Peroxisome proliferator-activated receptor-gamma agonists may improve adiposopathy through recruitment of functional fat cells and apoptosis of dysfunctional fat cells.

body organs (ie, hepatomegaly and splenomegaly), as well as adverse clinical consequences including shortness of breath, fatigue, and pulmonary/peripheral edema. "Adiposopathy" is adipose tissue disease wherein, anatomically, positive caloric balance in susceptible patients an underlying pathophysiologic process that leads to excessive fat-related metabolic diseases (EFRMD), such as T2DM, hypertension, and dyslipidemia [5]—all cardiovascular disease (CVD) risk factors—as well as potentially leading to atherosclerosis itself (Table 1) [1,6••].

HIGHER ORDER HEALTH

PPAR-Gamma Agonists

- Fatty acids (omega-3, 6, 9)
- Curcumin
- EGCG
- N-Acetylcysteine
- Lipoic Acid
- Thymoquinone
- Quercetin
- Astralagus
- Glycyrrhiza
- Ginger



HIGHER ORDER HEALTH


HIGHER ORDER
HEALTH

OVERVIEW

1. It’s about balance
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6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

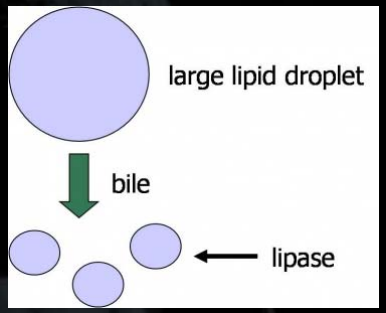
HIGHER ORDER HEALTH

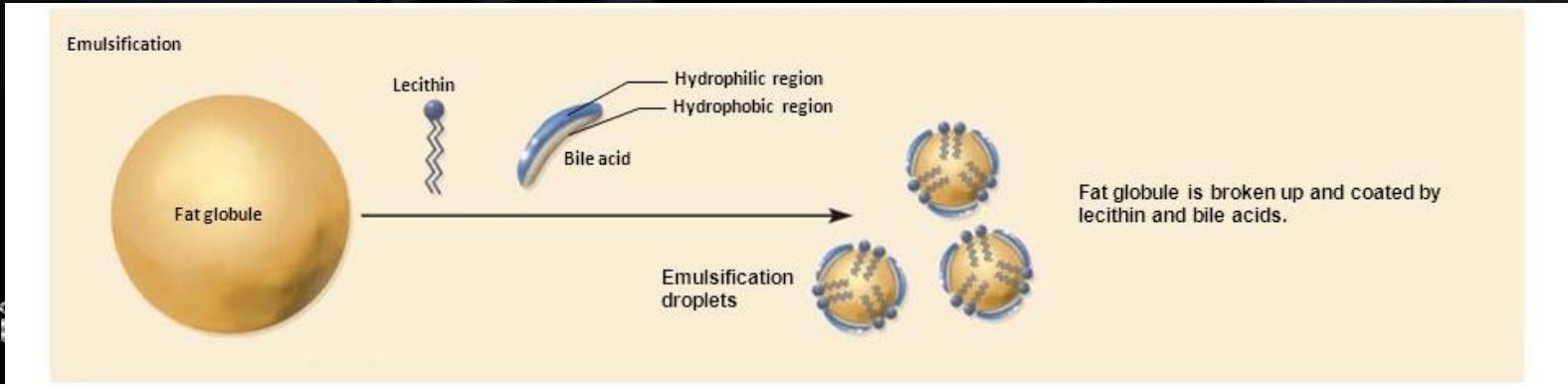
New Hormones

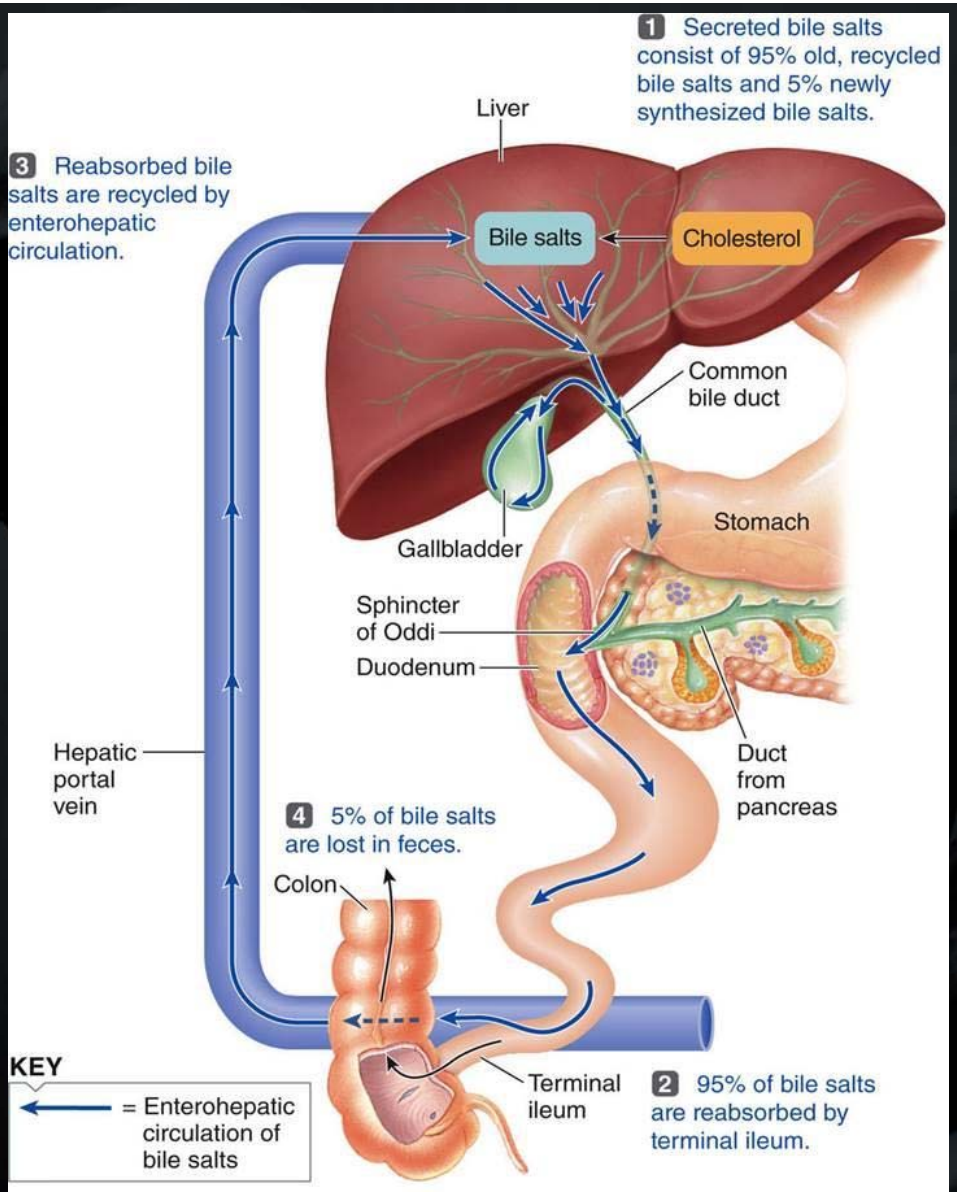
HIGHER ORDER HEALTH

The Story of Bile

- When lipids are consumed, the enteroendocrine cells (I cells) release CCK, which stimulates gall bladder contraction
- Bile serves to emulsify fat globule* and form micelles for transport and absorption of fatty acids

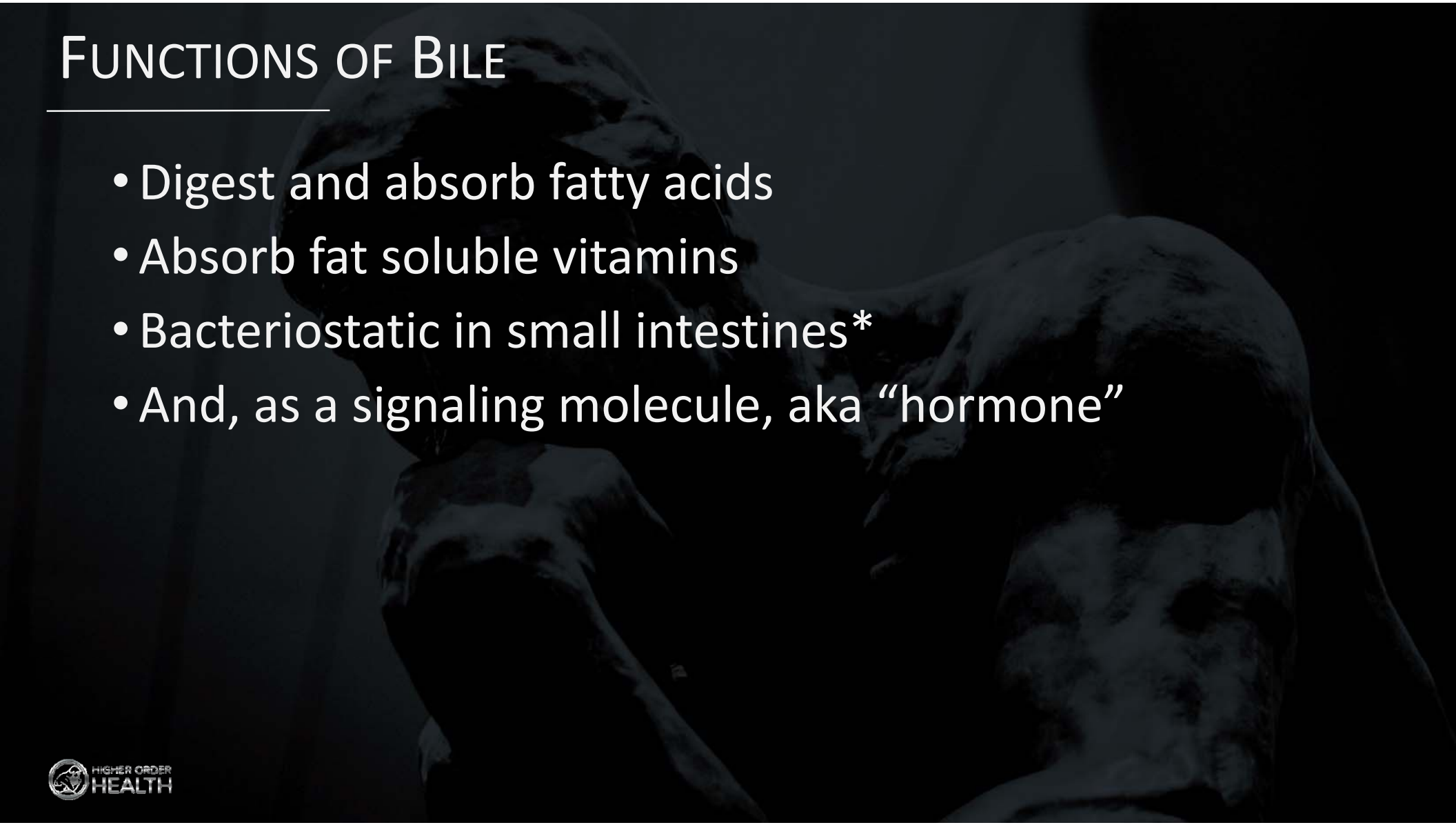






Functions of Bile

- Digest and absorb fatty acids
- Absorb fat soluble vitamins
- Bacteriostatic in small intestines*
- And, as a signaling molecule, aka “hormone”

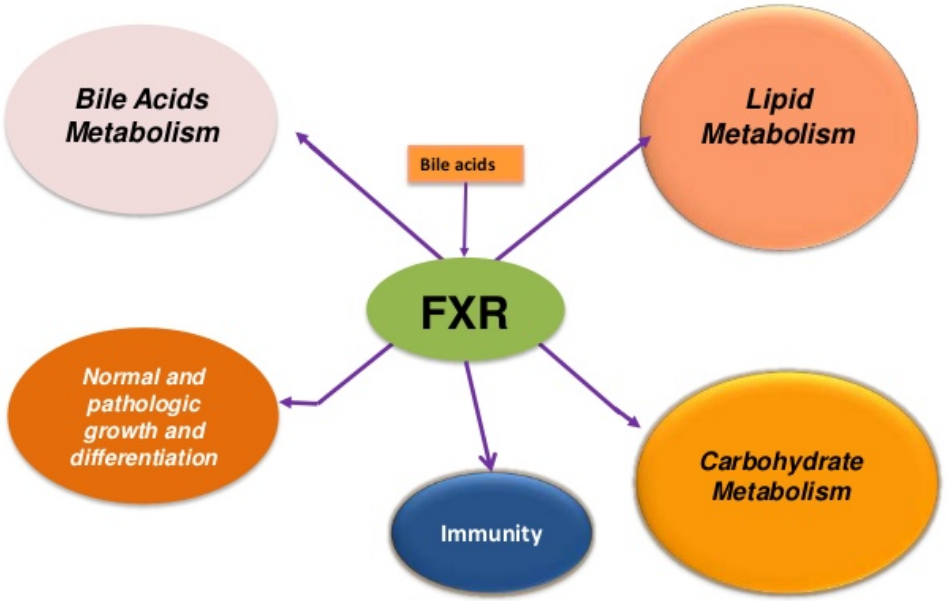


HIGHER ORDER HEALTH

FXR AND TGR5 RECEPTORS

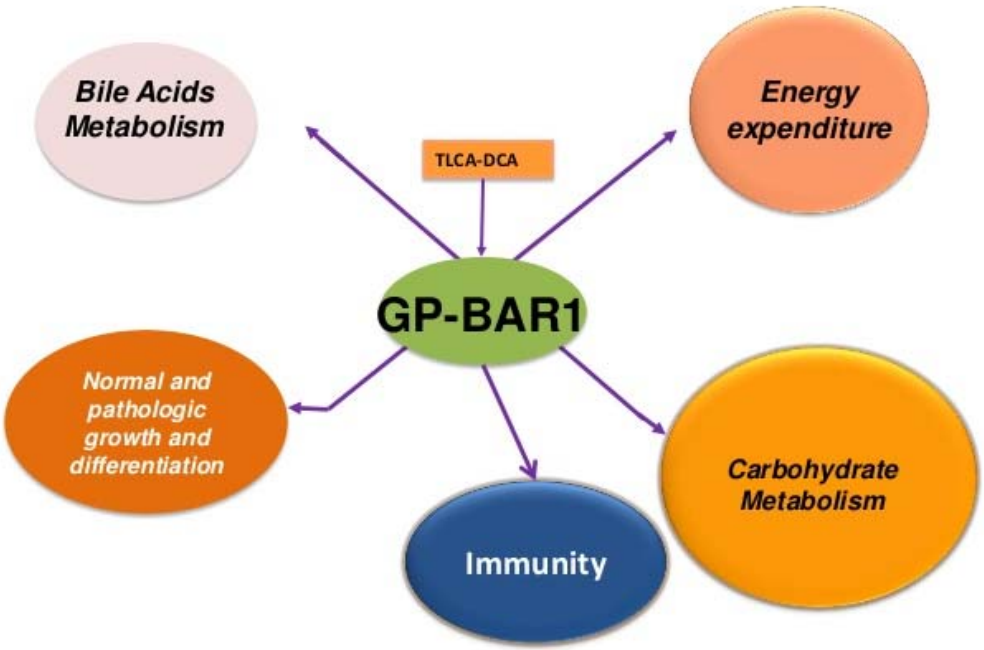
- Farnesoid X Receptor (FXR)
  - Also known as Bile Acid Receptor
  - Nuclear receptor
  - Found in liver, intestine, kidney and adrenal gland (also adipose and heart)
  - Regulates bile acid synthesis, conjugation and transport, glucose and lipid homeostasis, liver regeneration
- TGR5
  - Also known as membrane-type receptor for bile acids (M-BAR)
  - Membrane receptor
  - Ubiquitous – found in endocrine glands, adipocytes, muscles, spleen, lymph nodes, brain, spinal cord, enteric nervous system
  - Involved in bile acid metabolism, inflammation, glucose metabolism, energy metabolism

FXR is central to bile acids signaling



Fiorucci S., et al. Prog Lipid Res. 2010 Apr;49(2):171-85

GP-BAR1 (TGR5, M-BAR1)



HIGHER ORDER HEALTH

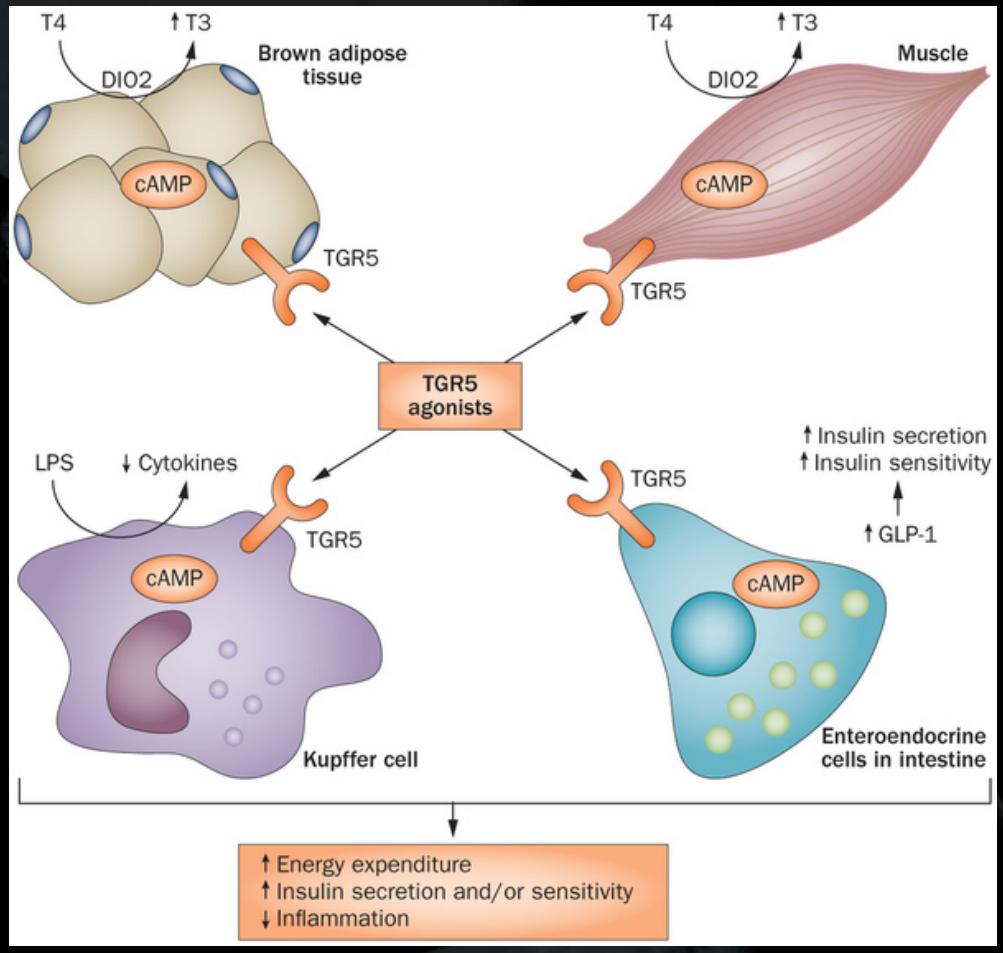
Bile Acids and Fat Loss

- Bacterial balance
- Improved glucose and lipid regulation (FXR)
- Increased GLP-1
- Increased energy expenditure (TGR5)
  - Receptor high in brown fat and skeletal muscle
  - Increases fatty acid oxidation and metabolic rate
  - Increases conversion of T4 to T3

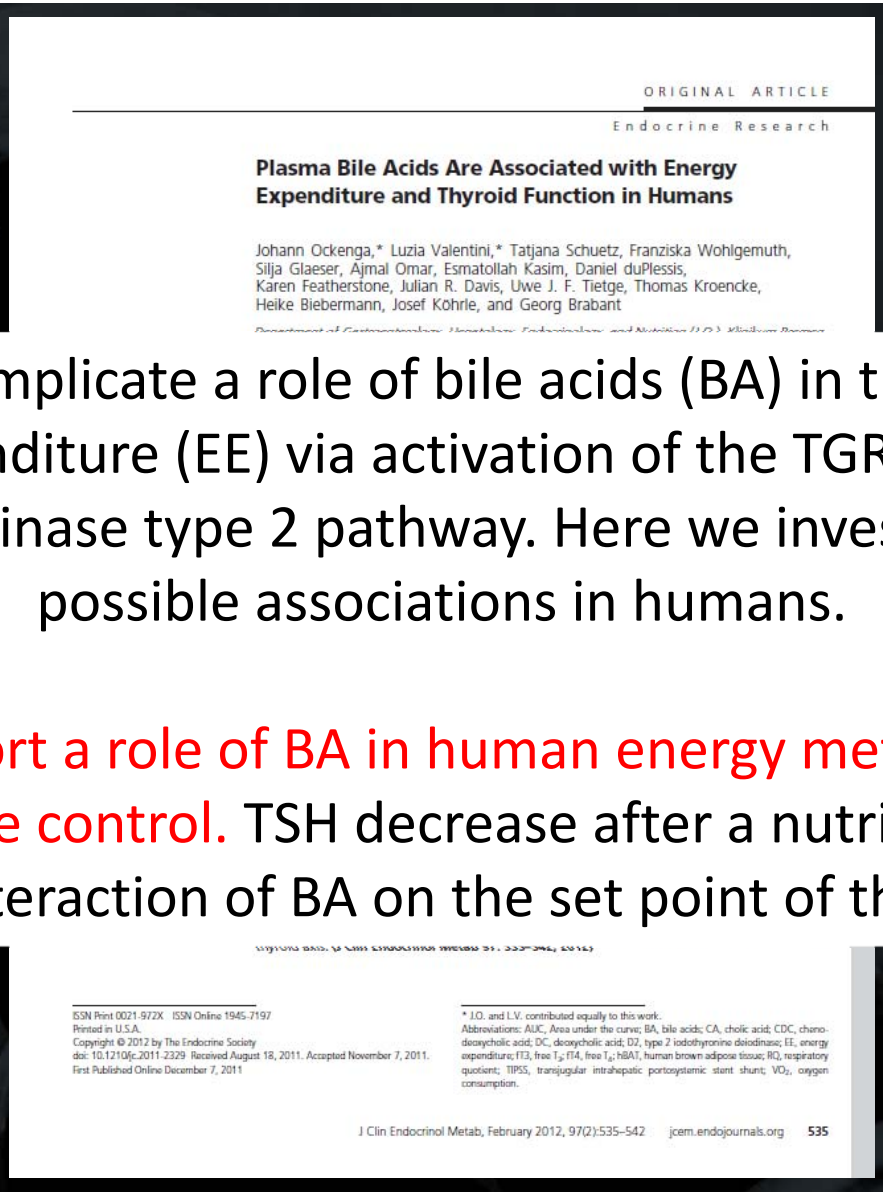
Bile Increases Energy Expenditure

Bile acids increases energy expenditure and oxygen consumption (TGR5)

- In brown adipocytes and skeletal muscle, activates iodotyrosine deiodinase (D2), which increases conversion of T4 to T3



HIGHER ORDER HEALTH



ORIGINAL ARTICLE

Endocrine Research

Plasma Bile Acids Are Associated with Energy Expenditure and Thyroid Function in Humans

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Animal studies implicate a role of bile acids (BA) in thyroid-regulated energy expenditure (EE) via activation of the TGR-5/adenylate cyclase/deiodinase type 2 pathway. Here we investigated these possible associations in humans.

Our data support a role of BA in human energy metabolism and in thyroid hormone control. TSH decrease after a nutritional challenge suggests an interaction of BA on the set point of the thyroid axis.

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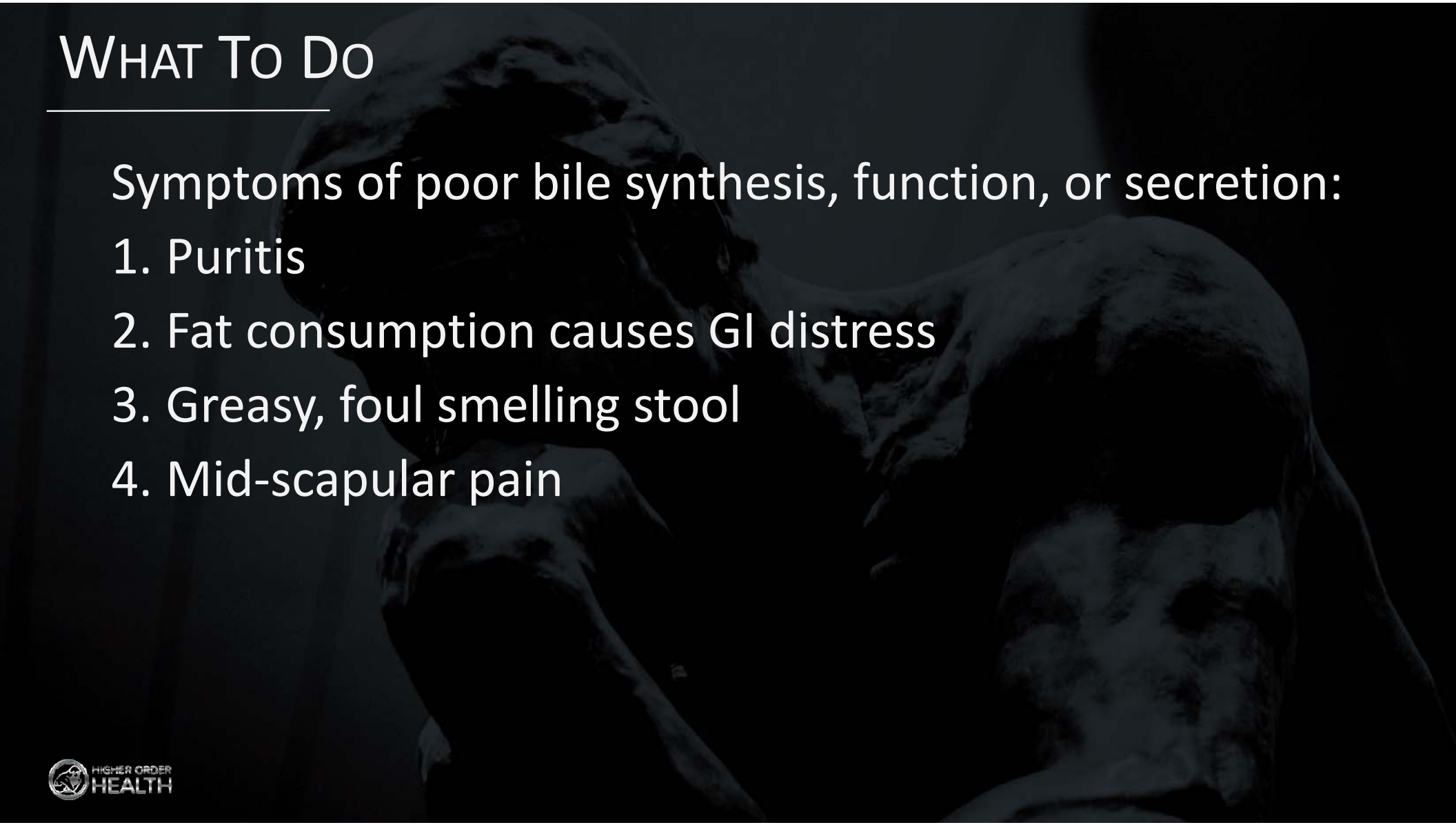
Abbreviations: AUC, Area under the curve; BA, bile acids; CA, cholic acid; CDC, chenodeoxycholic acid; DC, deoxycholic acid; D2, type 2 iodothyronine deiodinase; EE, energy expenditure; fT3, free T_3; fT4, free T_4; hBAT, human brown adipose tissue; RQ, respiratory quotient; TIPSS, transjugular intrahepatic portosystemic stent shunt; VO_2, oxygen consumption.

HIGHER ORDER HEALTH

What To Do

Symptoms of poor bile synthesis, function, or secretion:

1. Puritis
2. Fat consumption causes GI distress
3. Greasy, foul smelling stool
4. Mid-scapular pain



HIGHER ORDER HEALTH

What To Do

- Choleretics/Cholegogues
  - Dandelion root
  - Chamomile
  - Yarrow
  - Rosemary
  - Chelidonium
  - Taurine/glycine
- Ox bile
  - 10-15 mg/kg/day considered safe (ursodeoxycholic acid)
  - 500-1000 mg


HIGHER ORDER
HEALTH

OVERVIEW

1. It’s about balance
2. Where’s the problem?
3. Gut health and hormones
4. Chemical toxins and hormones
5. Can we have sick fat cells?
6. New hormones (that didn’t used to be hormones)
7. Perception and hormones

HIGHER ORDER HEALTH

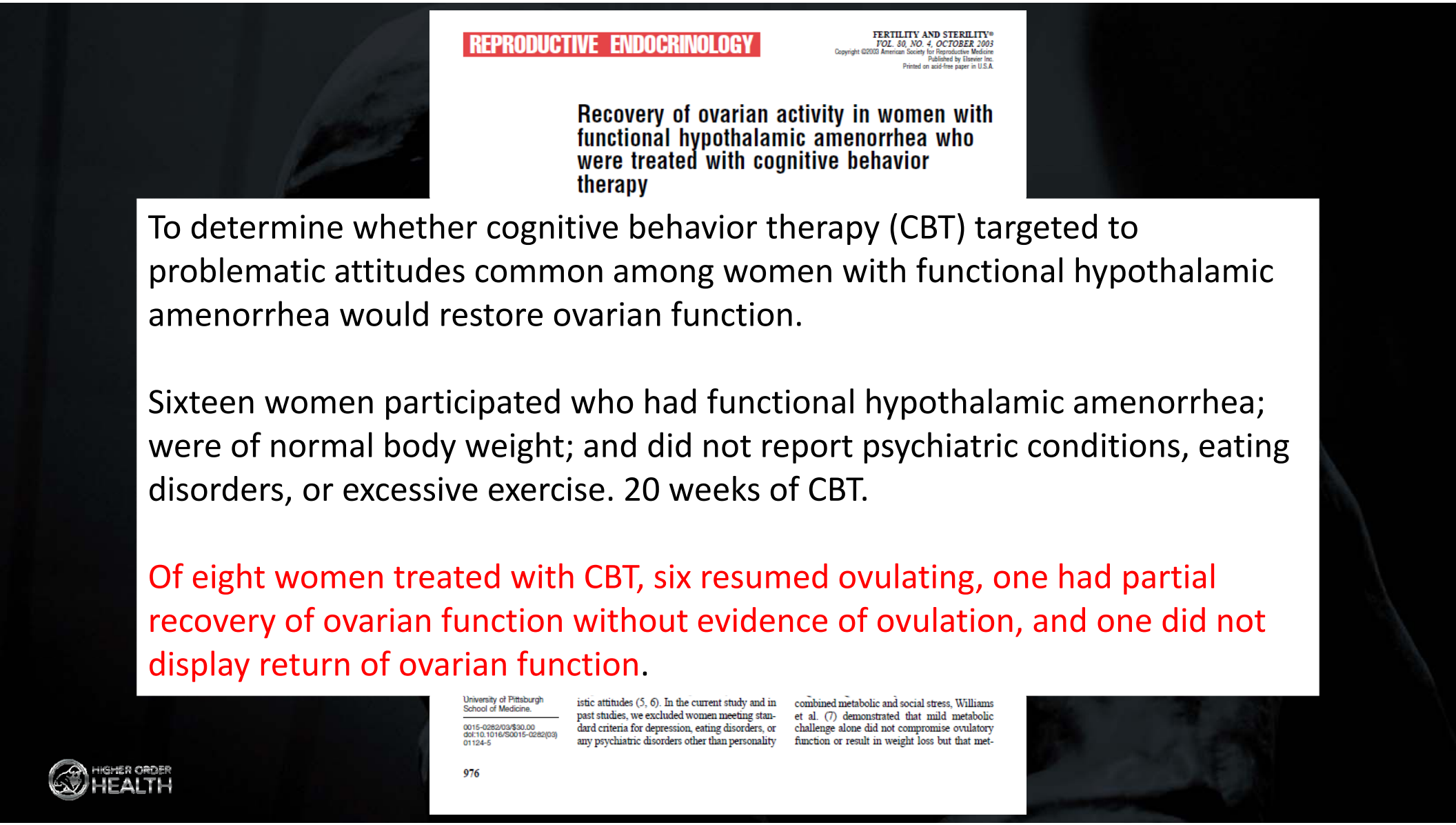
Perception & Evolution

HIGHER ORDER HEALTH

On 2 separate occasions, participants (n=46) consumed a 380-calorie milkshake under the pretense that it was either a 620-calorie “indulgent” shake or a 140-calorie “sensible” shake. Ghrelin was measured via intravenous blood samples at 3 time points: baseline (20 min), anticipatory (60 min), and postconsumption (90 min).

During the first interval (between 20 and 60 min) participants were asked to view and rate the
(misleading) label of the shake. During the second interval (between 60 and 90 min) participants were asked to drink and rate the milkshake.

The mindset of indulgence produced a dramatically steeper decline in ghrelin after consuming the shake, whereas the mindset of sensibility produced a relatively flat ghrelin response. Participants’ satiety was consistent with what they believed they were consuming rather than the actual nutritional value of what they consumed.



REPRODUCTIVE ENDOCRINOLOGY

FERTILITY AND STERILITY®
VOL. 80, NO. 4, OCTOBER 2003

Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy

To determine whether cognitive behavior therapy (CBT) targeted to problematic attitudes common among women with functional hypothalamic amenorrhea would restore ovarian function.

Sixteen women participated who had functional hypothalamic amenorrhea; were of normal body weight; and did not report psychiatric conditions, eating disorders, or excessive exercise. 20 weeks of CBT.

Of eight women treated with CBT, six resumed ovulating, one had partial recovery of ovarian function without evidence of ovulation, and one did not display return of ovarian function.

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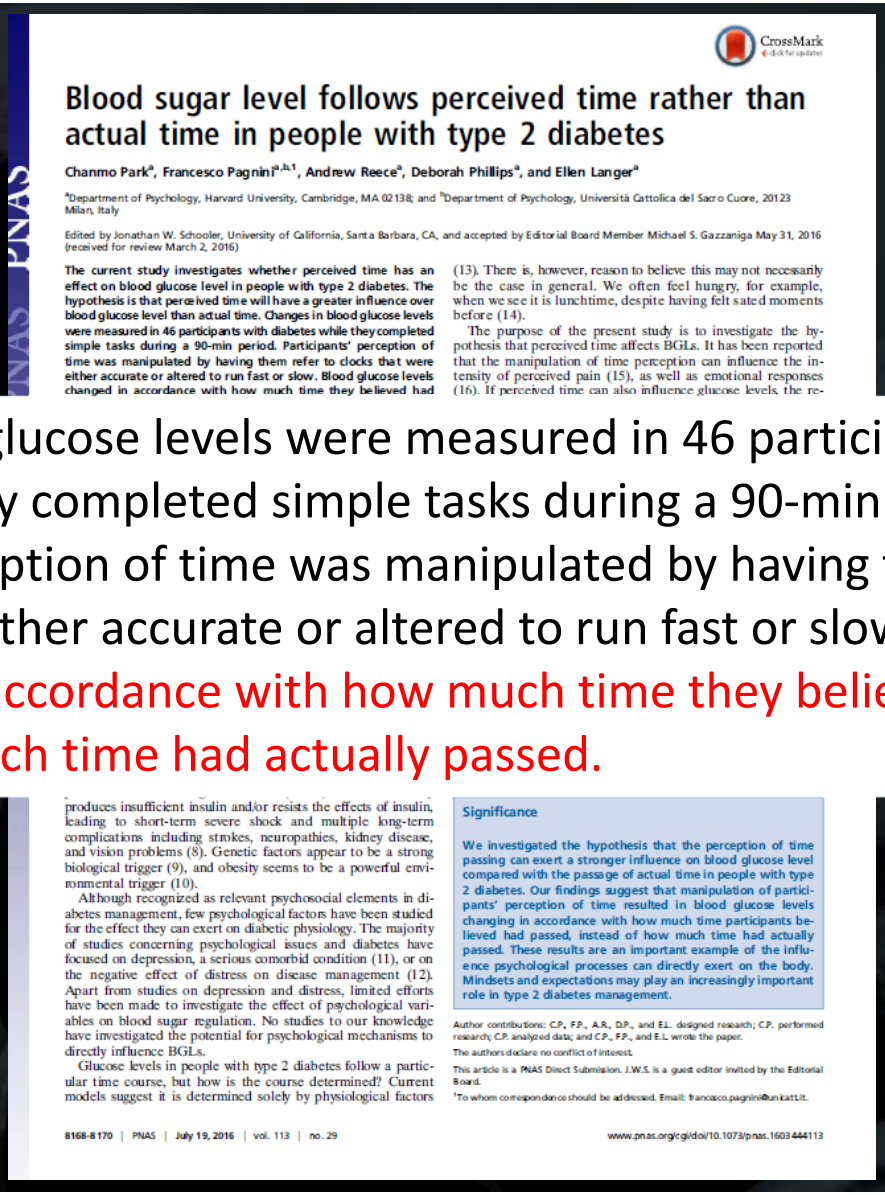
istic attitudes (5, 6). In the current study and in past studies, we excluded women meeting standard criteria for depression, eating disorders, or any psychiatric disorders other than personality

combined metabolic and social stress, Williams et al. (7) demonstrated that mild metabolic challenge alone did not compromise ovulatory function or result in weight loss but that met-

HIGHER ORDER HEALTH



Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes

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The current study investigates whether perceived time has an effect on blood glucose level in people with type 2 diabetes. The hypothesis is that perceived time will have a greater influence over blood glucose level than actual time. Changes in blood glucose levels were measured in 46 participants with diabetes while they completed simple tasks during a 90-min period. Participants' perception of time was manipulated by having them refer to clocks that were either accurate or altered to run fast or slow. Blood glucose levels changed in accordance with how much time they believed had

(13). There is, however, reason to believe this may not necessarily be the case in general. We often feel hungry, for example, when we see it is lunchtime, despite having felt sated moments before (14).

The purpose of the present study is to investigate the hypothesis that perceived time affects BGLs. It has been reported that the manipulation of time perception can influence the intensity of perceived pain (15), as well as emotional responses (16). If perceived time can also influence glucose levels, the re-

Changes in blood glucose levels were measured in 46 participants with diabetes while they completed simple tasks during a 90-min period. Participants' perception of time was manipulated by having them refer to clocks that were either accurate or altered to run fast or slow. Blood glucose levels changed in accordance with how much time they believed had passed instead of how much time had actually passed.

produces insufficient insulin and/or resists the effects of insulin, leading to short-term severe shock and multiple long-term complications including strokes, neuropathies, kidney disease, and vision problems (8). Genetic factors appear to be a strong biological trigger (9), and obesity seems to be a powerful environmental trigger (10).

Although recognized as relevant psychosocial elements in diabetes management, few psychological factors have been studied for the effect they can exert on diabetic physiology. The majority of studies concerning psychological issues and diabetes have focused on depression, a serious comorbid condition (11), or on the negative effect of distress on disease management (12). Apart from studies on depression and distress, limited efforts have been made to investigate the effect of psychological variables on blood sugar regulation. No studies to our knowledge have investigated the potential for psychological mechanisms to directly influence BGLs.

Glucose levels in people with type 2 diabetes follow a particular time course, but how is the course determined? Current models suggest it is determined solely by physiological factors

Significance

We investigated the hypothesis that the perception of time passing can exert a stronger influence on blood glucose level compared with the passage of actual time in people with type 2 diabetes. Our findings suggest that manipulation of participants' perception of time resulted in blood glucose levels changing in accordance with how much time participants believed had passed, instead of how much time had actually passed. These results are an important example of the influence psychological processes can directly exert on the body. Mindsets and expectations may play an increasingly important role in type 2 diabetes management.

Author contributions: C.P., F.P., A.R., D.P., and E.L. designed research; C.P. performed research; C.P. analyzed data; and C.P., F.P., and E.L. wrote the paper.

The authors declare no conflict of interest.

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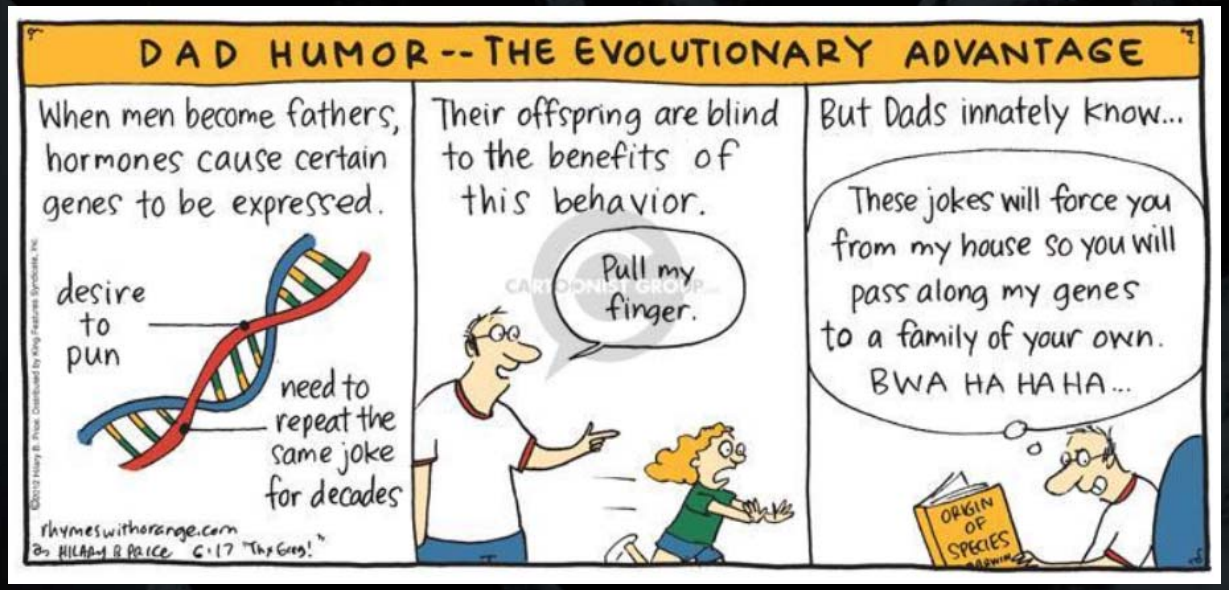
Perception & Evolution



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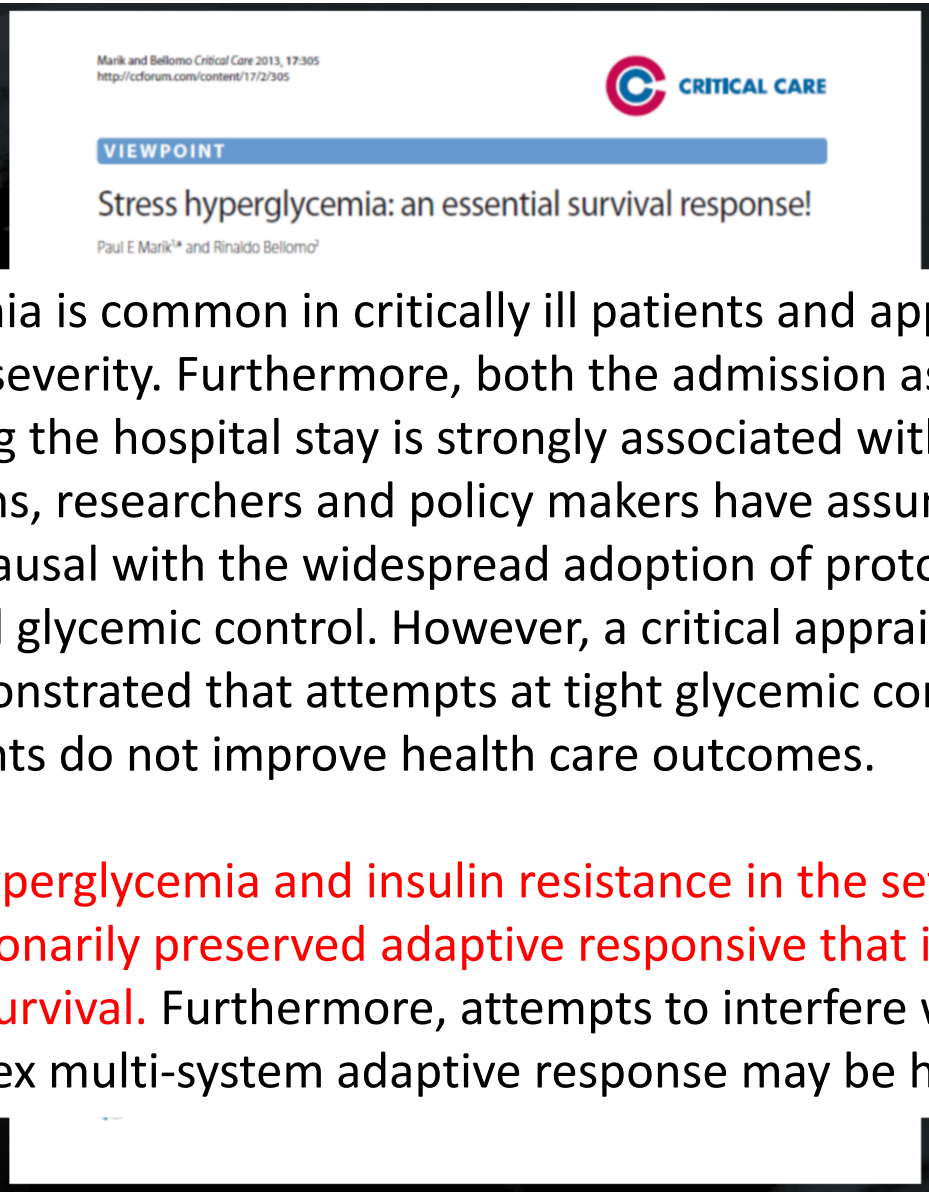

Marik and Bellomo *Critical Care* 2013, 17:305
http://ccforum.com/content/17/2/305

CRITICAL CARE

VIEWPOINT

Stress hyperglycemia: an essential survival response!

Paul E Marik[1]* and Rinaldo Bellomo[2]

Stress hyperglycemia is common in critically ill patients and appears to be a marker of disease severity. Furthermore, both the admission as well as the mean glucose level during the hospital stay is strongly associated with patient outcomes. Clinicians, researchers and policy makers have assumed this association to be causal with the widespread adoption of protocols and programs for tight in-hospital glycemic control. However, a critical appraisal of the literature has demonstrated that attempts at tight glycemic control in both ICU and non-ICU patients do not improve health care outcomes.

We suggest that hyperglycemia and insulin resistance in the setting of acute illness is an evolutionarily preserved adaptive responsive that increases the host's chances of survival. Furthermore, attempts to interfere with this exceedingly complex multi-system adaptive response may be harmful.

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The Molecular-Genetic Basis of Functional Hyperandrogenism and the Polycystic Ovary Syndrome

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Insulin resistance increases glucose availability for brain metabolism. It also increases salt and water retention and sympathetic tone and induces endothelial dysfunction, favoring an increase in blood pressure, obviously beneficial when trauma occurs. Similarly, the increased coagulability and decreased fibrinolysis associated with insulin resistance are defensive mechanisms against bleeding. But more important is that insulin resistance favors obesity, protecting against starvation, and obesity contributes to a proinflammatory state through the secretion of several cytokines, contributing to the defense against infection, and possibly to the development of functional hyperandrogenism and PCOS.

VI. Hyperandrogenism, PCOS, and Survival Advantage

First Published Online November 23, 2004

Abbreviations: AR, Androgen receptor; CRP, C-reactive protein; CYP, cytochrome P450; gp130, gp130 subunit of IL-6 receptor; HSD, hydroxysteroid dehydrogenase; INS, insulin gene; INSR, insulin receptor gene; IRS, insulin receptor substrate; LHβ, β-subunit of LH; PAI-1, plasminogen activator inhibitor-1; PCOS, polycystic ovary syndrome; PON1, paraoxonase; PPAR-γ2, peroxisome proliferator-activated receptor-γ2; SORBS1, human homolog for the sorbin and SH3-domain-containing 1 gene; SNP, single nucleotide polymorphism; SRD5A, steroid 5α-reductase; TNFR2, type 2 TNF receptor; VNTR, variable number of tandem repeats.

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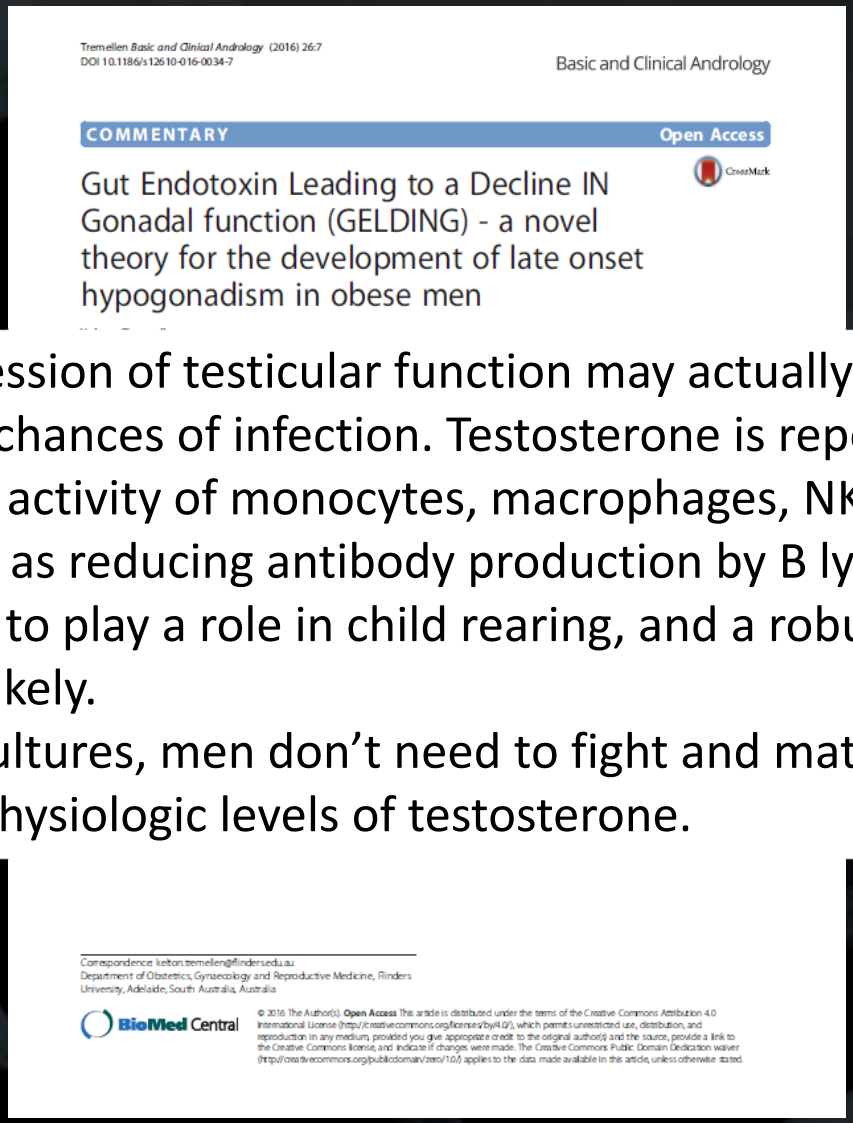
toms such as hirsutism, acne, and/or alopecia; menstrual irregularity; and, in a significant proportion of patients, insulin resistance (3).

The presence of male sexual secondary characteristics in women has been recognized from ancient times, but it was not until 1921 when Achard and Thyers (4) reported the association of hyperandrogenic symptoms with abnormalities in glucose metabolism, highlighting the presence of polycystic ovaries in some of their patients. However, only after the description of seven cases of amenorrhea and bilateral polycystic ovaries by Stein and Leventhal in 1935 (5) was PCOS considered a separate entity that interested clinicians and researchers worldwide.

Although for many years the interest in PCOS has been



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DOI 10.1186/s12610-016-0034-7

Basic and Clinical Andrology

COMMENTARY Open Access

Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING) - a novel theory for the development of late onset hypogonadism in obese men

Inflammatory suppression of testicular function may actually be an adaptive response, to reduce chances of infection. Testosterone is reported to dampen the immuno-stimulatory activity of monocytes, macrophages, NK cells, T lymphocytes, as well as reducing antibody production by B lymphocytes

- Men are expected to play a role in child rearing, and a robust immune system makes that more likely.
- In monogamous cultures, men don't need to fight and mate, and therefore don't need supraphysiologic levels of testosterone.

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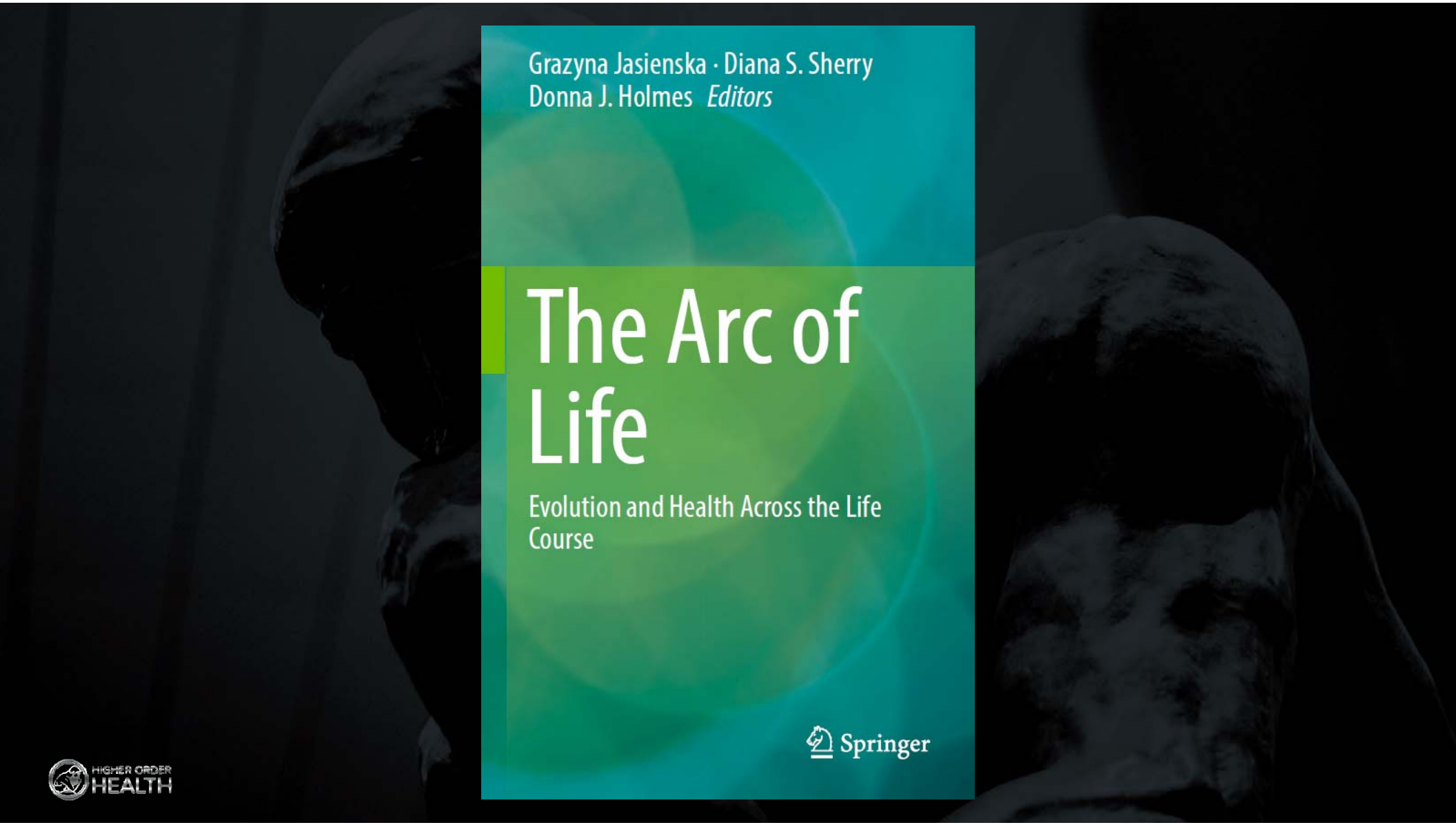
Grazyna Jasienska · Diana S. Sherry
Donna J. Holmes Editors
The Arc of Life
Evolution and Health Across the Life Course
Springer
HIGHER ORDER HEALTH

The Arc Of Life

- Individuals inhabiting high pathogen-risk environments may benefit from decreased testosterone levels to avoid immunosuppression and suspend energetically expensive anabolic functions
- Estradiol and other estrogens appear to be immunostimulatory. Higher circulating estrogen levels in women compared to men may help explain why females typically exhibit higher CD4+ helper T cell Th-2 cytokine responses greater B cell function, lowered rates of cellular apoptosis, enhanced cellular proliferation, and greater antibody secretion, all of which may translate into lower morbidity and mortality from infectious diseases

Human Immunity is Energetically Expensive

- Severe perturbations like sepsis, burns, trauma, and surgery are associated with a 25–55 % increase in resting metabolic rate compared with that in healthy subjects
- Fever typically results in a 7–15 % increase in resting metabolic rate for every 1 °C rise in body temperature
- For example, in a sample of 25 nonfebrile young men naturally infected with respiratory tract pathogens, resting metabolic rate was elevated by 14 % compared to samples taken after convalescence

HIGHER ORDER HEALTH


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Is it about hormones?
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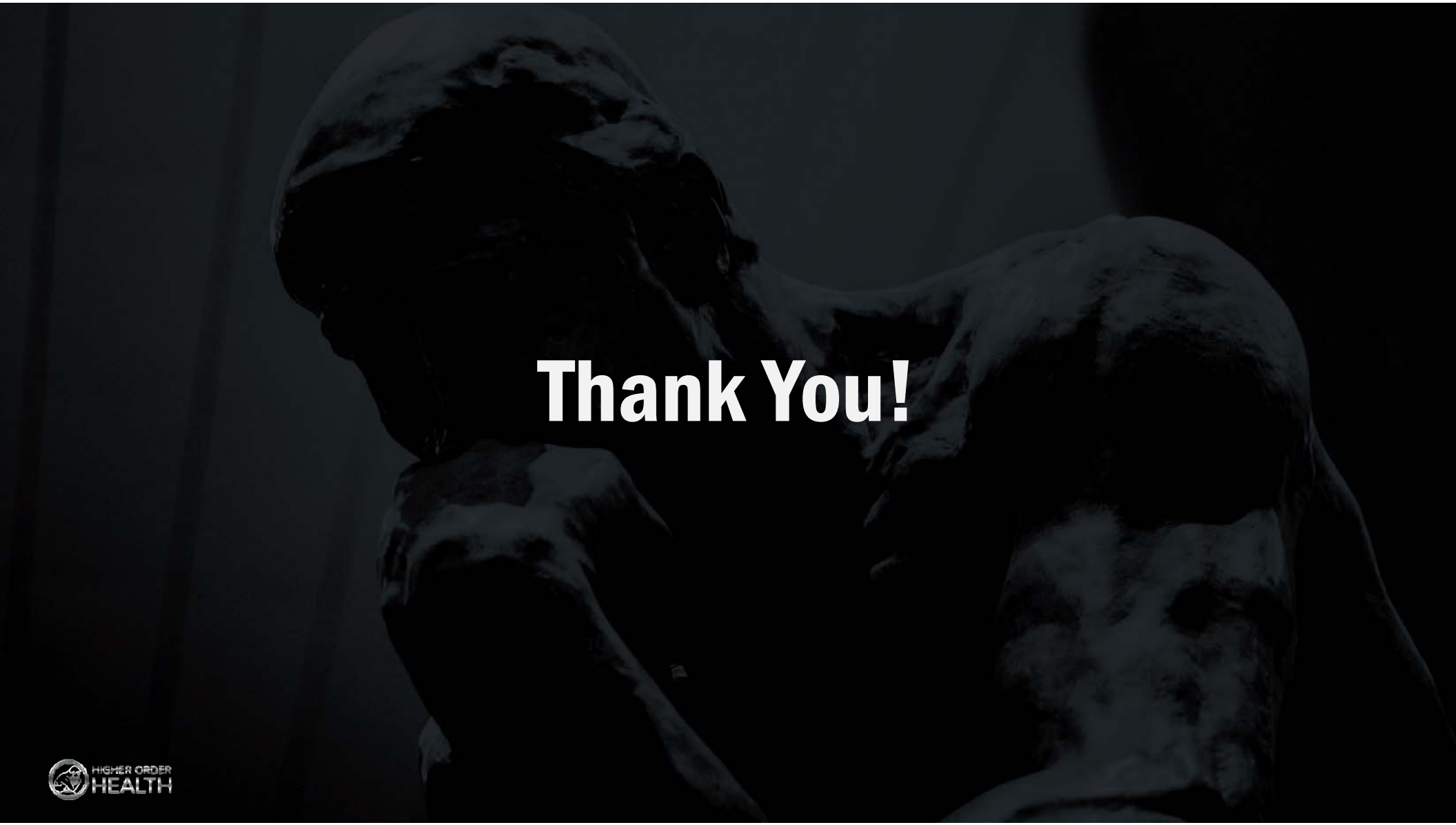
HEALTH


Thank You!
HIGHER ORDER
HEALTH